

= Enzyme inhibitor =

An enzyme inhibitor is a molecule that binds to an enzyme and decreases its activity . Since blocking an enzyme 's activity can kill a pathogen or correct a metabolic imbalance , many drugs are enzyme inhibitors . They are also used in pesticides . Not all molecules that bind to enzymes are inhibitors ; enzyme activators bind to enzymes and increase their enzymatic activity , while enzyme substrates bind and are converted to products in the normal catalytic cycle of the enzyme .

The binding of an inhibitor can stop a substrate from entering the enzyme 's active site and / or hinder the enzyme from catalyzing its reaction . Inhibitor binding is either reversible or irreversible . Irreversible inhibitors usually react with the enzyme and change it chemically (e.g. via covalent bond formation) . These inhibitors modify key amino acid residues needed for enzymatic activity . In contrast , reversible inhibitors bind non @-@ covalently and different types of inhibition are produced depending on whether these inhibitors bind to the enzyme , the enzyme @-@ substrate complex , or both .

Many drug molecules are enzyme inhibitors , so their discovery and improvement is an active area of research in biochemistry and pharmacology . A medicinal enzyme inhibitor is often judged by its specificity (its lack of binding to other proteins) and its potency (its dissociation constant , which indicates the concentration needed to inhibit the enzyme) . A high specificity and potency ensure that a drug will have few side effects and thus low toxicity .

Enzyme inhibitors also occur naturally and are involved in the regulation of metabolism . For example , enzymes in a metabolic pathway can be inhibited by downstream products . This type of negative feedback slows the production line when products begin to build up and is an important way to maintain homeostasis in a cell . Other cellular enzyme inhibitors are proteins that specifically bind to and inhibit an enzyme target . This can help control enzymes that may be damaging to a cell , like proteases or nucleases . A well @-@ characterised example of this is the ribonuclease inhibitor , which binds to ribonucleases in one of the tightest known protein ? protein interactions . Natural enzyme inhibitors can also be poisons and are used as defences against predators or as ways of killing prey .

= = Reversible inhibitors = =

= = = Types of reversible inhibitors = = =

Reversible inhibitors attach to enzymes with non @-@ covalent interactions such as hydrogen bonds , hydrophobic interactions and ionic bonds . Multiple weak bonds between the inhibitor and the active site combine to produce strong and specific binding . In contrast to substrates and irreversible inhibitors , reversible inhibitors generally do not undergo chemical reactions when bound to the enzyme and can be easily removed by dilution or dialysis .

There are four kinds of reversible enzyme inhibitors . They are classified according to the effect of varying the concentration of the enzyme 's substrate on the inhibitor .

In competitive inhibition , the substrate and inhibitor cannot bind to the enzyme at the same time , as shown in the figure on the right . This usually results from the inhibitor having an affinity for the active site of an enzyme where the substrate also binds ; the substrate and inhibitor compete for access to the enzyme 's active site . This type of inhibition can be overcome by sufficiently high concentrations of substrate (V_{max} remains constant) , i.e. , by out @-@ competing the inhibitor . However , the apparent K_m will increase as it takes a higher concentration of the substrate to reach the K_m point , or half the V_{max} . Competitive inhibitors are often similar in structure to the real substrate (see examples below) .

In uncompetitive inhibition , the inhibitor binds only to the substrate @-@ enzyme complex , it should not be confused with non @-@ competitive inhibitors . This type of inhibition causes V_{max} to decrease (maximum velocity decreases as a result of removing activated complex) and K_m to decrease (due to better binding efficiency as a result of Le Chatelier 's principle and the effective

elimination of the ES complex thus decreasing the K_m which indicates a higher binding affinity) .

In non @-@ competitive inhibition , the binding of the inhibitor to the enzyme reduces its activity but does not affect the binding of substrate . As a result , the extent of inhibition depends only on the concentration of the inhibitor . V_{max} will decrease due to the inability for the reaction to proceed as efficiently , but K_m will remain the same as the actual binding of the substrate , by definition , will still function properly .

In mixed inhibition , the inhibitor can bind to the enzyme at the same time as the enzyme 's substrate . However , the binding of the inhibitor affects the binding of the substrate , and vice versa . This type of inhibition can be reduced , but not overcome by increasing concentrations of substrate . Although it is possible for mixed @-@ type inhibitors to bind in the active site , this type of inhibition generally results from an allosteric effect where the inhibitor binds to a different site on an enzyme . Inhibitor binding to this allosteric site changes the conformation (i.e. , tertiary structure or three @-@ dimensional shape) of the enzyme so that the affinity of the substrate for the active site is reduced .

= = = Quantitative description of reversible inhibition = = =

Reversible inhibition can be described quantitatively in terms of the inhibitor 's binding to the enzyme and to the enzyme @-@ substrate complex , and its effects on the kinetic constants of the enzyme . In the classic Michaelis @-@ Menten scheme below , an enzyme (E) binds to its substrate (S) to form the enzyme ? substrate complex ES . Upon catalysis , this complex breaks down to release product P and free enzyme . The inhibitor (I) can bind to either E or ES with the dissociation constants K_i or K_i' , respectively .

When an enzyme has multiple substrates , inhibitors can show different types of inhibition depending on which substrate is considered . This results from the active site containing two different binding sites within the active site , one for each substrate . For example , an inhibitor might compete with substrate A for the first binding site , but be a non @-@ competitive inhibitor with respect to substrate B in the second binding site .

= = = Measuring the dissociation constants of a reversible inhibitor = = =

As noted above , an enzyme inhibitor is characterised by its two dissociation constants , K_i and K_i' , to the enzyme and to the enzyme @-@ substrate complex , respectively . The enzyme @-@ inhibitor constant K_i can be measured directly by various methods ; one extremely accurate method is isothermal titration calorimetry , in which the inhibitor is titrated into a solution of enzyme and the heat released or absorbed is measured . However , the other dissociation constant K_i' is difficult to measure directly , since the enzyme @-@ substrate complex is short @-@ lived and undergoing a chemical reaction to form the product . Hence , K_i' is usually measured indirectly , by observing the enzyme activity under various substrate and inhibitor concentrations , and fitting the data to a modified Michaelis ? Menten equation

<formula>

where the modifying factors ? and ? ' are defined by the inhibitor concentration and its two dissociation constants

<formula>

<formula>

Thus , in the presence of the inhibitor , the enzyme 's effective K_m and V_{max} become (? / ? ') K_m and (1 / ? ') V_{max} , respectively . However , the modified Michaelis @-@ Menten equation assumes that binding of the inhibitor to the enzyme has reached equilibrium , which may be a very slow process for inhibitors with sub @-@ nanomolar dissociation constants . In these cases , it is usually more practical to treat the tight @-@ binding inhibitor as an irreversible inhibitor (see below) ; however , it can still be possible to estimate K_i' kinetically if K_i is measured independently .

The effects of different types of reversible enzyme inhibitors on enzymatic activity can be visualized using graphical representations of the Michaelis ? Menten equation , such as Lineweaver ? Burk

and Eadie v_0/v_0^0 Hofstee plots . For example , in the Lineweaver ? Burk plots at the right , the competitive inhibition lines intersect on the y v_0/v_0^0 axis , illustrating that such inhibitors do not affect V_{max} . Similarly , the non v_0/v_0^0 competitive inhibition lines intersect on the x v_0/v_0^0 axis , showing these inhibitors do not affect K_m . However , it can be difficult to estimate K_i and K_i' accurately from such plots , so it is advisable to estimate these constants using more reliable nonlinear regression methods , as described above .

== Reversible inhibitors ==

Traditionally reversible enzyme inhibitors have been classified as competitive , uncompetitive , or non v_0/v_0^0 competitive , according to their effects on K_m and V_{max} . These different effects result from the inhibitor binding to the enzyme E , to the enzyme ? substrate complex ES , or to both , respectively . The division of these classes arises from a problem in their derivation and results in the need to use two different binding constants for one binding event . The binding of an inhibitor and its effect on the enzymatic activity are two distinctly different things , another problem the traditional equations fail to acknowledge . In noncompetitive inhibition the binding of the inhibitor results in 100 % inhibition of the enzyme only , and fails to consider the possibility of anything in between . The common form of the inhibitory term also obscures the relationship between the inhibitor binding to the enzyme and its relationship to any other binding term be it the Michaelis ? Menten equation or a dose response curve associated with ligand receptor binding . To demonstrate the relationship the following rearrangement can be made :

<formula>

Adding zero to the bottom ($[I] - [I]$)

<formula>

Dividing by $[I] + K_i$

<formula>

This notation demonstrates that similar to the Michaelis ? Menten equation , where the rate of reaction depends on the percent of the enzyme population interacting with substrate .

fraction of the enzyme population bound by substrate

<formula>

fraction of the enzyme population bound by inhibitor

<formula>

the effect of the inhibitor is a result of the percent of the enzyme population interacting with inhibitor . The only problem with this equation in its present form is that it assumes absolute inhibition of the enzyme with inhibitor binding , when in fact there can be a wide range of effects anywhere from 100 % inhibition of substrate turn over to just > 0 % . To account for this the equation can be easily modified to allow for different degrees of inhibition by including a ΔV_{max} term .

<formula>

or

<formula>

This term can then define the residual enzymatic activity present when the inhibitor is interacting with individual enzymes in the population . However the inclusion of this term has the added value of allowing for the possibility of activation if the secondary V_{max} term turns out to be higher than the initial term . To account for the possibly of activation as well the notation can then be rewritten replacing the inhibitor " I " with a modifier term denoted here as " X " .

<formula>

While this terminology results in a simplified way of dealing with kinetic effects relating to the maximum velocity of the Michaelis ? Menten equation , it highlights potential problems with the term used to describe effects relating to the K_m . The K_m relating to the affinity of the enzyme for the substrate should in most cases relate to potential changes in the binding site of the enzyme which would directly result from enzyme inhibitor interactions . As such a term similar to the one proposed above to modulate V_{max} should be appropriate in most situations :

<formula>

=== Special cases ===

The mechanism of partially competitive inhibition is similar to that of non-competitive, except that the EIS complex has catalytic activity, which may be lower or even higher (partially competitive activation) than that of the enzyme-substrate (ES) complex. This inhibition typically displays a lower V_{max} , but an unaffected K_m value.

Uncompetitive inhibition occurs when the inhibitor binds only to the enzyme-substrate complex, not to the free enzyme; the EIS complex is catalytically inactive. This mode of inhibition is rare and causes a decrease in both V_{max} and the K_m value.

Substrate and product inhibition is where either the substrate or product of an enzyme reaction inhibit the enzyme's activity. This inhibition may follow the competitive, uncompetitive or mixed patterns. In substrate inhibition there is a progressive decrease in activity at high substrate concentrations. This may indicate the existence of two substrate-binding sites in the enzyme. At low substrate, the high-affinity site is occupied and normal kinetics are followed. However, at higher concentrations, the second inhibitory site becomes occupied, inhibiting the enzyme. Product inhibition is often a regulatory feature in metabolism and can be a form of negative feedback.

Slow-tight inhibition occurs when the initial enzyme-inhibitor complex EI undergoes isomerisation to a second more tightly held complex, EI^* , but the overall inhibition process is reversible. This manifests itself as slowly increasing enzyme inhibition. Under these conditions, traditional Michaelis-Menten kinetics give a false value for K_i , which is time-dependent. The true value of K_i can be obtained through more complex analysis of the on (k_{on}) and off (k_{off}) rate constants for inhibitor association. See irreversible inhibition below for more information.

=== Examples of reversible inhibitors ===

As enzymes have evolved to bind their substrates tightly, and most reversible inhibitors bind in the active site of enzymes, it is unsurprising that some of these inhibitors are strikingly similar in structure to the substrates of their targets. An example of these substrate mimics are the protease inhibitors, a very successful class of antiretroviral drugs used to treat HIV. The structure of ritonavir, a protease inhibitor based on a peptide and containing three peptide bonds, is shown on the right. As this drug resembles the protein that is the substrate of the HIV protease, it competes with this substrate in the enzyme's active site.

Enzyme inhibitors are often designed to mimic the transition state or intermediate of an enzyme-catalyzed reaction. This ensures that the inhibitor exploits the transition state stabilising effect of the enzyme, resulting in a better binding affinity (lower K_i) than substrate-based designs. An example of such a transition state inhibitor is the antiviral drug oseltamivir; this drug mimics the planar nature of the ring oxonium ion in the reaction of the viral enzyme neuraminidase.

However, not all inhibitors are based on the structures of substrates. For example, the structure of another HIV protease inhibitor, tipranavir, is shown on the left. This molecule is not based on a peptide and has no obvious structural similarity to a protein substrate. These non-peptide inhibitors can be more stable than inhibitors containing peptide bonds, because they will not be substrates for peptidases and are less likely to be degraded.

In drug design it is important to consider the concentrations of substrates to which the target enzymes are exposed. For example, some protein kinase inhibitors have chemical structures that are similar to adenosine triphosphate, one of the substrates of these enzymes. However, drugs that are simple competitive inhibitors will have to compete with the high concentrations of ATP in the cell. Protein kinases can also be inhibited by competition at the binding sites where the kinases interact with their substrate proteins, and most proteins are present inside cells at concentrations much lower than the concentration of ATP. As a consequence, if two protein kinase inhibitors both bind in the active site with similar affinity, but only one has to compete with ATP, then the competitive inhibitor at the protein-binding site will inhibit the enzyme more effectively.

= = Irreversible inhibitors = =

= = = Types of irreversible inhibition = = =

Irreversible inhibitors usually covalently modify an enzyme, and inhibition can therefore not be reversed. Irreversible inhibitors often contain reactive functional groups such as nitrogen mustards, aldehydes, haloalkanes, alkenes, Michael acceptors, phenyl sulfonates, or fluorophosphonates. These electrophilic groups react with amino acid side chains to form covalent adducts. The residues modified are those with side chains containing nucleophiles such as hydroxyl or sulfhydryl groups; these include the amino acids serine (as in DFP, right), cysteine, threonine, or tyrosine.

Irreversible inhibition is different from irreversible enzyme inactivation. Irreversible inhibitors are generally specific for one class of enzyme and do not inactivate all proteins; they do not function by destroying protein structure but by specifically altering the active site of their target. For example, extremes of pH or temperature usually cause denaturation of all protein structure, but this is a non-specific effect. Similarly, some non-specific chemical treatments destroy protein structure: for example, heating in concentrated hydrochloric acid will hydrolyse the peptide bonds holding proteins together, releasing free amino acids.

Irreversible inhibitors display time-dependent inhibition and their potency therefore cannot be characterised by an IC_{50} value. This is because the amount of active enzyme at a given concentration of irreversible inhibitor will be different depending on how long the inhibitor is pre-incubated with the enzyme. Instead, $k_{obs} / [I]$ values are used, where k_{obs} is the observed pseudo-first order rate of inactivation (obtained by plotting the log of % activity vs. time) and $[I]$ is the concentration of inhibitor. The $k_{obs} / [I]$ parameter is valid as long as the inhibitor does not saturate binding with the enzyme (in which case $k_{obs} = k_{inact}$).

= = = Analysis of irreversible inhibition = = =

As shown in the figure to the left, irreversible inhibitors form a reversible non-covalent complex with the enzyme (EI or ESI) and this then reacts to produce the covalently modified "dead" end complex "EI*". The rate at which EI* is formed is called the inactivation rate or k_{inact} . Since formation of EI may compete with ES, binding of irreversible inhibitors can be prevented by competition either with substrate or with a second, reversible inhibitor. This protection effect is good evidence of a specific reaction of the irreversible inhibitor with the active site.

The binding and inactivation steps of this reaction are investigated by incubating the enzyme with inhibitor and assaying the amount of activity remaining over time. The activity will be decreased in a time-dependent manner, usually following exponential decay. Fitting these data to a rate equation gives the rate of inactivation at this concentration of inhibitor. This is done at several different concentrations of inhibitor. If a reversible EI complex is involved the inactivation rate will be saturable and fitting this curve will give k_{inact} and K_i .

Another method that is widely used in these analyses is mass spectrometry. Here, accurate measurement of the mass of the unmodified native enzyme and the inactivated enzyme gives the increase in mass caused by reaction with the inhibitor and shows the stoichiometry of the reaction. This is usually done using a MALDI-TOF mass spectrometer. In a complementary technique, peptide mass fingerprinting involves digestion of the native and modified protein with a protease such as trypsin. This will produce a set of peptides that can be analysed using a mass spectrometer. The peptide that changes in mass after reaction with the inhibitor will be the one that contains the site of modification.

= = = Special cases = = =

Not all irreversible inhibitors form covalent adducts with their enzyme targets. Some reversible

inhibitors bind so tightly to their target enzyme that they are essentially irreversible . These tight @-@ binding inhibitors may show kinetics similar to covalent irreversible inhibitors . In these cases , some of these inhibitors rapidly bind to the enzyme in a low @-@ affinity EI complex and this then undergoes a slower rearrangement to a very tightly bound EI * complex (see figure above) . This kinetic behaviour is called slow @-@ binding . This slow rearrangement after binding often involves a conformational change as the enzyme " clamps down " around the inhibitor molecule . Examples of slow @-@ binding inhibitors include some important drugs , such methotrexate , allopurinol , and the activated form of acyclovir .

= = = Examples of irreversible inhibitors = = =

Diisopropylfluorophosphate (DFP) is shown as an example of an irreversible protease inhibitor in the figure above right . The enzyme hydrolyses the phosphorus ? fluorine bond , but the phosphate residue remains bound to the serine in the active site , deactivating it . Similarly , DFP also reacts with the active site of acetylcholine esterase in the synapses of neurons , and consequently is a potent neurotoxin , with a lethal dose of less than 100 mg .

Suicide inhibition is an unusual type of irreversible inhibition where the enzyme converts the inhibitor into a reactive form in its active site . An example is the inhibitor of polyamine biosynthesis , ? @-@ difluoromethylornithine or DFMO , which is an analogue of the amino acid ornithine , and is used to treat African trypanosomiasis (sleeping sickness) . Ornithine decarboxylase can catalyse the decarboxylation of DFMO instead of ornithine , as shown above . However , this decarboxylation reaction is followed by the elimination of a fluorine atom , which converts this catalytic intermediate into a conjugated imine , a highly electrophilic species . This reactive form of DFMO then reacts with either a cysteine or lysine residue in the active site to irreversibly inactivate the enzyme .

Since irreversible inhibition often involves the initial formation of a non @-@ covalent EI complex , it is sometimes possible for an inhibitor to bind to an enzyme in more than one way . For example , in the figure showing trypanothione reductase from the human protozoan parasite *Trypanosoma cruzi* , two molecules of an inhibitor called quinacrine mustard are bound in its active site . The top molecule is bound reversibly , but the lower one is bound covalently as it has reacted with an amino acid residue through its nitrogen mustard group .

= = Discovery and design of inhibitors = =

New drugs are the products of a long drug development process , the first step of which is often the discovery of a new enzyme inhibitor . In the past the only way to discover these new inhibitors was by trial and error : screening huge libraries of compounds against a target enzyme and hoping that some useful leads would emerge . This brute force approach is still successful and has even been extended by combinatorial chemistry approaches that quickly produce large numbers of novel compounds and high @-@ throughput screening technology to rapidly screen these huge chemical libraries for useful inhibitors .

More recently , an alternative approach has been applied : rational drug design uses the three @-@ dimensional structure of an enzyme 's active site to predict which molecules might be inhibitors . These predictions are then tested and one of these tested compounds may be a novel inhibitor . This new inhibitor is then used to try to obtain a structure of the enzyme in an inhibitor / enzyme complex to show how the molecule is binding to the active site , allowing changes to be made to the inhibitor to try to optimise binding . This test and improve cycle is then repeated until a sufficiently potent inhibitor is produced . Computer @-@ based methods of predicting the affinity of an inhibitor for an enzyme are also being developed , such as molecular docking and molecular mechanics .

= = Uses of inhibitors = =

Enzyme inhibitors are found in nature and are also designed and produced as part of pharmacology and biochemistry . Natural poisons are often enzyme inhibitors that have evolved to defend a plant

or animal against predators . These natural toxins include some of the most poisonous compounds known . Artificial inhibitors are often used as drugs , but can also be insecticides such as malathion , herbicides such as glyphosate , or disinfectants such as triclosan . Other artificial enzyme inhibitors block acetylcholinesterase , an enzyme which breaks down acetylcholine , and are used as nerve agents in chemical warfare .

== Chemotherapy ==

The most common uses for enzyme inhibitors are as drugs to treat disease . Many of these inhibitors target a human enzyme and aim to correct a pathological condition . However , not all drugs are enzyme inhibitors . Some , such as anti @-@ epileptic drugs , alter enzyme activity by causing more or less of the enzyme to be produced . These effects are called enzyme induction and inhibition and are alterations in gene expression , which is unrelated to the type of enzyme inhibition discussed here . Other drugs interact with cellular targets that are not enzymes , such as ion channels or membrane receptors .

An example of a medicinal enzyme inhibitor is sildenafil (Viagra) , a common treatment for male erectile dysfunction . This compound is a potent inhibitor of cGMP specific phosphodiesterase type 5 , the enzyme that degrades the signalling molecule cyclic guanosine monophosphate . This signalling molecule triggers smooth muscle relaxation and allows blood flow into the corpus cavernosum , which causes an erection . Since the drug decreases the activity of the enzyme that halts the signal , it makes this signal last for a longer period of time .

Another example of the structural similarity of some inhibitors to the substrates of the enzymes they target is seen in the figure comparing the drug methotrexate to folic acid . Folic acid is a substrate of dihydrofolate reductase , an enzyme involved in making nucleotides that is potentially inhibited by methotrexate . Methotrexate blocks the action of dihydrofolate reductase and thereby halts the production of nucleotides . This block of nucleotide biosynthesis is more toxic to rapidly growing cells than non @-@ dividing cells , since a rapidly growing cell has to carry out DNA replication , therefore methotrexate is often used in cancer chemotherapy .

== Antibiotics ==

Drugs also are used to inhibit enzymes needed for the survival of pathogens . For example , bacteria are surrounded by a thick cell wall made of a net @-@ like polymer called peptidoglycan . Many antibiotics such as penicillin and vancomycin inhibit the enzymes that produce and then cross @-@ link the strands of this polymer together . This causes the cell wall to lose strength and the bacteria to burst . In the figure , a molecule of penicillin (shown in a ball @-@ and @-@ stick form) is shown bound to its target , the transpeptidase from the bacteria *Streptomyces* R61 (the protein is shown as a ribbon @-@ diagram) .

Antibiotic drug design is facilitated when an enzyme that is essential to the pathogen 's survival is absent or very different in humans . In the example above , humans do not make peptidoglycan , therefore inhibitors of this process are selectively toxic to bacteria . Selective toxicity is also produced in antibiotics by exploiting differences in the structure of the ribosomes in bacteria , or how they make fatty acids .

== Metabolic control ==

Enzyme inhibitors are also important in metabolic control . Many metabolic pathways in the cell are inhibited by metabolites that control enzyme activity through allosteric regulation or substrate inhibition . A good example is the allosteric regulation of the glycolytic pathway . This catabolic pathway consumes glucose and produces ATP , NADH and pyruvate . A key step for the regulation of glycolysis is an early reaction in the pathway catalysed by phosphofructokinase @-@ 1 (PFK1) . When ATP levels rise , ATP binds an allosteric site in PFK1 to decrease the rate of the enzyme reaction ; glycolysis is inhibited and ATP production falls . This negative feedback control helps

maintain a steady concentration of ATP in the cell . However , metabolic pathways are not just regulated through inhibition since enzyme activation is equally important . With respect to PFK1 , fructose 2 ,6 -bisphosphate and ADP are examples of metabolites that are allosteric activators .

Physiological enzyme inhibition can also be produced by specific protein inhibitors . This mechanism occurs in the pancreas , which synthesises many digestive precursor enzymes known as zymogens . Many of these are activated by the trypsin protease , so it is important to inhibit the activity of trypsin in the pancreas to prevent the organ from digesting itself . One way in which the activity of trypsin is controlled is the production of a specific and potent trypsin inhibitor protein in the pancreas . This inhibitor binds tightly to trypsin , preventing the trypsin activity that would otherwise be detrimental to the organ . Although the trypsin inhibitor is a protein , it avoids being hydrolysed as a substrate by the protease by excluding water from trypsin 's active site and destabilising the transition state . Other examples of physiological enzyme inhibitor proteins include the barstar inhibitor of the bacterial ribonuclease barnase and the inhibitors of protein phosphatases .

== Pesticides ==

Many pesticides are enzyme inhibitors . Acetylcholinesterase (AChE) is an enzyme found in animals from insects to humans . It is essential to nerve cell function through its mechanism of breaking down the neurotransmitter acetylcholine into its constituents , acetate and choline . This is somewhat unique among neurotransmitters as most , including serotonin , dopamine , and norepinephrine , are absorbed from the synaptic cleft rather than cleaved . A large number of AChE inhibitors are used in both medicine and agriculture . Reversible competitive inhibitors , such as edrophonium , physostigmine , and neostigmine , are used in the treatment of myasthenia gravis and in anaesthesia . The carbamate pesticides are also examples of reversible AChE inhibitors . The organophosphate pesticides such as malathion , parathion , and chlorpyrifos irreversibly inhibit acetylcholinesterase .

The herbicide glyphosate is an inhibitor of 3 -phosphoshikimate 1 -carboxyvinyltransferase , other herbicides , such as the sulfonylureas inhibit the enzyme acetolactate synthase . Both these enzymes are needed for plants to make branched chain amino acids . Many other enzymes are inhibited by herbicides , including enzymes needed for the biosynthesis of lipids and carotenoids and the processes of photosynthesis and oxidative phosphorylation .

== Natural poisons ==

Animals and plants have evolved to synthesise a vast array of poisonous products including secondary metabolites , peptides and proteins that can act as inhibitors . Natural toxins are usually small organic molecules and are so diverse that there are probably natural inhibitors for most metabolic processes . The metabolic processes targeted by natural poisons encompass more than enzymes in metabolic pathways and can also include the inhibition of receptor , channel and structural protein functions in a cell . For example , paclitaxel (taxol) , an organic molecule found in the Pacific yew tree , binds tightly to tubulin dimers and inhibits their assembly into microtubules in the cytoskeleton .

Many natural poisons act as neurotoxins that can cause paralysis leading to death and have functions for defence against predators or in hunting and capturing prey . Some of these natural inhibitors , despite their toxic attributes , are valuable for therapeutic uses at lower doses . An example of a neurotoxin are the glycoalkaloids , from the plant species in the Solanaceae family (includes potato , tomato and eggplant) , that are acetylcholinesterase inhibitors . Inhibition of this enzyme causes an uncontrolled increase in the acetylcholine neurotransmitter , muscular paralysis and then death . Neurotoxicity can also result from the inhibition of receptors ; for example , atropine from deadly nightshade (*Atropa belladonna*) that functions as a competitive antagonist of the muscarinic acetylcholine receptors .

Although many natural toxins are secondary metabolites , these poisons also include peptides and proteins . An example of a toxic peptide is alpha -amanitin , which is found in relatives of the death cap mushroom . This is a potent enzyme inhibitor , in this case preventing the RNA polymerase II enzyme from transcribing DNA . The algal toxin microcystin is also a peptide and is an inhibitor of protein phosphatases . This toxin can contaminate water supplies after algal blooms and is a known carcinogen that can also cause acute liver hemorrhage and death at higher doses .

Proteins can also be natural poisons or antinutrients , such as the trypsin inhibitors (discussed above) that are found in some legumes , as shown in the figure above . A less common class of toxins are toxic enzymes : these act as irreversible inhibitors of their target enzymes and work by chemically modifying their substrate enzymes . An example is ricin , an extremely potent protein toxin found in castor oil beans . This enzyme is a glycosidase that inactivates ribosomes . Since ricin is a catalytic irreversible inhibitor , this allows just a single molecule of ricin to kill a cell .