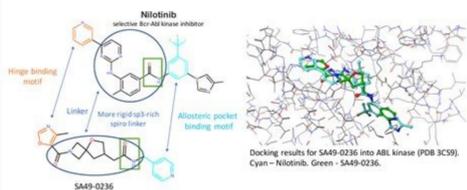


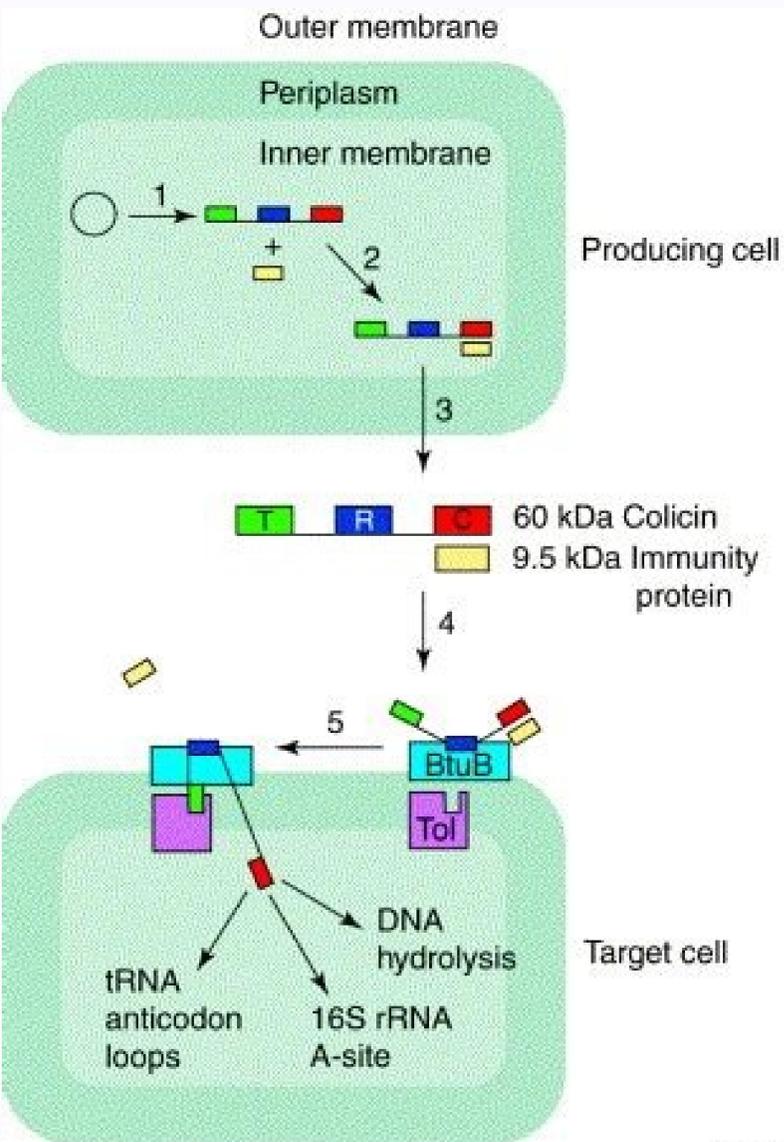
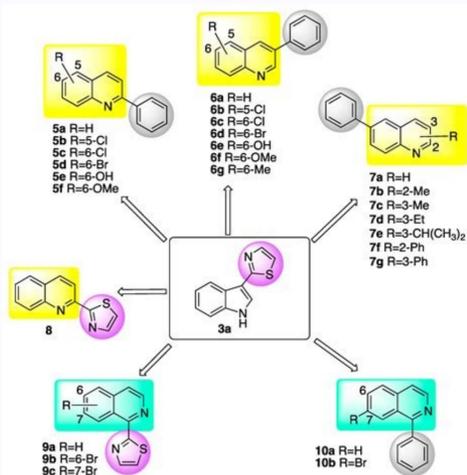
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Methodology. Similarity and molecular docking.
Inhibitor Type II as an example.

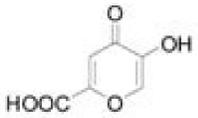


Competitive inhibition	Non competitive	Irreversible inhibition	Allosteric inhibition	Suicide inhibition	Feedback inhibition
Structural similarity to S	No structural similarity	Bind tightly to E by covalent bonds	I binds to Allosteric site of the E	I makes use of the E's own Rn mechanism to inactivate it	End products inhibits earlier E of the metabolic pathway
Compete with S for active site	Do not compete. Binds to site different from active site	Cause conformational change in active site of E			
Inc. S removes E	Rn slowed down				
Km - Inc. Vmax - no change	Km - no change Vmax - dec.	Km - no change Vmax - dec.	Km - inc. Vmax - dec.		
Drugs: Sulfonamides, Statins, Methotrexate	Heavy metal poisons	Cyanide, OP poisoning, Iodoacetate	PFK-1 - ATP and Citrate	Allopurinol, Fluorouracil	Heme - ALA synthase Cholesterol - HMG-CoA reductase

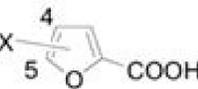


Class I

Sr. No.	X	Cell-based IC ₅₀ (µM)	Enzyme-based IC ₅₀ (µM)
2.	H	9.0	405
8.	Br	10.0	---



Sr. No.	X	Cell-based IC ₅₀ (µM)	Enzyme-based IC ₅₀ (µM)
10.	---	15.0	103 (K _i = 61 µM; lactate inhibitor)



Class II

Sr. No.	X	Cell-based IC ₅₀ (µM)	Enzyme-based IC ₅₀ (µM)
11.	4-COOH	60.0	160
13.	5-Br	>100	125

W.H. Freeman and Company, New-York, USA. In this case, there are two types of complexes: enzyme inhibitor (EI) and enzyme substrate (ES); complex EI has no enzyme activity. The increase of concentration of these compounds in the blood may be involved in the development of several cardiovascular and renal diseases including volume-expanded hypertension, chronic renal failure, and congestive heart failure [24]. Natural poisons are a powerful instrument for investigation of enzyme function, and analysis of their action is necessary for these studies. They have named "suicide inhibitors," because each serpin molecule can inactivate a single molecule of protease and kills itself during the process of protease inhibition. Considering enzyme inhibitors we should keep in mind that many living organisms are in the state of "chemical war." Fungi are fighting with bacteria for food using antibiotics. Therefore calmodulin is considered as a participant of calcium signal transduction pathway that provides ordering and prolongation of the effect of Ca²⁺ as a second messenger [34]. Inhibitors and activators (modulators) that bind to enzymes not in the active site but in special center located far enough from it have name allosteric modulators. Enzymes are able to accelerate chemical reaction dividing it into separate steps. Curr Pharm Des. One product of glycolysis is ATP. Their binding to allosteric sites induces the change of enzyme conformation that affects both the structure of active site and enzyme conformational mobility leading to the decrease or to the increase of enzyme activity. Small organic compounds like ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetracetic acid (EGTA) and ethylenediaminetetraacetic acid (EDTA) that are known as chelating agents bind these inhibitory cations and by this way can eliminate their inhibitory effect. Special group of activators can produce activation of target enzymes only after the formation of complex with another molecule. 2015;6:49. In this case, inhibitor binds to E or to ES complex. Irreversible inhibitors are generally specific for one class of enzymes and do not inactivate all proteins. [32]. Advertisement Enzyme activators are chemical compounds that increase a velocity of enzymatic reaction. Inhibition of ACE results in the decrease of angiotensin I concentration and in the relaxation of smooth muscles of vessels. They are inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase, an enzyme participating in cholesterol synthesis. 2010;10:1203-33. 1996;2(3):135-40. This group of compounds (the most prescribed drugs in the world, the oldest among them is aspirin) was successfully used for more than one century around the whole world for treatment of patients with fever, cardiovascular diseases, joint pain, etc. This inhibition may be reversed by the increase of substrate concentration. Inhibition: nomenclature and theory. In this case, V_{max} will decrease, but K_m will remain the same (Figure 1, C). In some cases, we can see mixed inhibition, when the inhibitor can bind to the enzyme at the same time as to enzyme-substrate complex. 2015;23(23):7353-8. DOI: 10.1080/1521654021382522. Kataoka M, Head JF, Seaton BA. Melittin binding causes a large calcium-dependent conformational change in calmodulin. Irreversible inhibitors usually react with the enzyme and change it chemically. The K_i values for these sphingosyl glucosides were about increased 5 times for the Gaucher type-1 enzymes from Ashkenazi-Jewish Gaucher disease type-1 patients. A reaction catalyzing by fumarate hydratase (A) and comparison of structure of fumarate (substrate of reaction) and maleate (enzyme competitive inhibitor) (B) [16]. Some reversible inhibitors bind so tightly to the enzyme that they are essentially irreversible. PMID: 1347701.19. Tsilikounas E, Rao T, Guthel WW, Bachovich WW. Interaction of irreversible inhibitor with enzyme is a bimolecular reaction: where E is enzyme, I is inhibitor, EI is complex of enzyme-inhibitor, and k₁ is a constant of the velocity of this reaction. However, usually the action of irreversible inhibitors is characterized by the constant of observed pseudo-first order reaction under conditions when concentration of inhibitor is significantly higher than concentration of the enzyme. [16]. Productive binding of one substrate molecule with two points of enzyme active site (A) and unproductive binding of two substrate molecules with the same site (B). Competitive inhibitors mainly interact with enzyme active site preventing binding of real substrate. 2016;11(10):e0162775. Mechanism of inhibitor and activator action on the enzyme activity includes a step of their binding to the enzyme, after which a step of the change of enzyme conformation often follows. Inhibitors are a good tool for study of enzyme reaction mechanisms. It can be competitive inhibition not only in relation to substrate but also to cofactors, as well as to activators. Kinetic test for reversible inhibitor classification. DOI: 10.1016/j.jmb.2014.05.016.34. Brini M, Caraffi E. Using these reagents, cysteines were revealed in the active sites of some dehydrogenase, cysteine protease, and other enzymes. The second approach is the application of reactive substrate analogs. By this way, c-AMP activity depends upon the c-AMP concentration in the cell. Advertisement Enzyme inhibitors and activators are a number of various chemical compounds that can slow down (or even stop) and activate enzymes, natural protein catalysts. DOI: 10.1073/pnas.0907054106.10. Oosterbaan RA, Kunst P, Cohen JA. It is used for cancer therapy [29]. New promising direction of anticancer therapy that is connected with suppression of protein kinases controlling the cellular response to DNA damage is now on the step of development. Special studies have shown that melittin structure imitates structure of some proteins (to be exact, some part of protein molecules) that can interact with target enzyme to provide their biological function [23]. Another example of natural inhibitors is cardiotonic steroids that were found initially in plants (dioxin, digitonin, ouabain) and in the mucus of toads (marinobufagenin, bufotoxin, etc.). CHF 38.00 * EUR 35.00 * USD 39.00 * Select Save over 20% compared to the individual article price. Nonsteroidal antiinflammatory drugs and their effects. DOI: 10.1002/bmb.2005.49403010419.17. Krowarsch D, Cierpicki T, Jelen F, Otlewski J. Endogenous digoxin-like factors: an overview of the history. 4th ed. They were selected during the evolution to stop many metabolic processes in organisms of victims that lead to their death. Poisons of plants and invertebrates were used as medicine drugs during thousands of years. The effect of reversible inhibitors is characterized by the constant of dissociation of EI complex that is equal to [E][I]/[EI] or k₁/k₂. Usually reversible inhibitor binds to the enzymes using non-covalent interactions such as hydrogen or ionic bonds. 2013;52:2050-67. But there are many other groups of drugs that are by nature of inhibitors of some enzymes; the following groups of enzyme inhibitors are developed now by pharmaceutical companies and have very important therapeutic significances [24]. Inhibitors of angiotensin-converting enzyme (ACE). Biochim Biophys Acta. The second step of catalysis of usual substrates leads to the hydrolysis of ester bond and to the release of the second product (C-terminal part of protein substrate). It is known that proteolytic enzymes of the gastrointestinal tract are secreted from the pancreas in an inactive form. Lehninger Principles of Biochemistry. Location of Ser-195 in active site of chymotrypsin was confirmed in investigation carried out later, and the origin of its high reactivity was revealed. It might be also a model for design of new inhibitors and activators that will imitate natural compounds with such properties. We have mentioned above nonsteroidal anti-inflammatory drugs that are the inhibitors of cyclooxygenase. Reactive serine residue of the protease active site that loses H⁺ and becomes nucleophilic one in the beginning of catalytic act attacks substrate peptide bond. Fundamental challenges in mechanistic enzymology: progress toward understanding the rate enhancement of enzyme. According to contemporary hypothesis, high conformational mobility of the enzymes allows them to adopt their active sites to substrate(s) and intermediates of the reaction in the best way [1, 2]. Reactions of this cycle produce reduced nicotinamide adenine dinucleotide reduced (NADH) and flavinadeninucleotide reduced (FADH₂), oxidation of which is coupled with massive production of ATP in mitochondria. Mainly this mode of inhibition is connected with the formation of covalent bond or hydrophobic interaction between enzyme and inhibitor. The ever changing moods of calmodulin: how structural plasticity entails transactional adaptability. This type of inhibition can be reduced, but not overcome by the increase of substrate concentrations. PMID: 19078048.6. Cleland WW. An irreversible inhibitor dissociates from this complex very slow because it is tightly bound to the enzyme. Numerous metabolic pathways are controlled by these specific compounds that are synthesized in organisms. If we will analyze the composition of these poisons, we can find in their content a lot of various enzyme inhibitors. They also can provide inhibition affecting the enzyme conformation. J Clin Rheumatol. In contrast, the cationic lipids, sphingosyl-O6- D-glucoside (glucosyl sphingosine) and its N-hexyl derivative, were noncompetitive inhibitors whose apparent K_i values for the normal enzyme were 30 and 0.25 pmol/l, respectively. IUBMB Life. So, we can refer some chemical compound to irreversible enzyme inhibitor, if after the formation of EI complex, the dilution of it with significant amount of water (100-200 excess) does not restore enzyme activity. Irreversible inhibitors display time-dependent loss of enzyme activity. Biochem J Article / Publication Details Published online: August 11, 2017 Issue release date: 1985 Number of Print Pages: 11 Number of Figures: 0 ISSN: 0013-9432 (Print) eISSN: 2504-2564 (Online) For additional information: Enzymes are very effective biological catalysts that accelerate almost all metabolic reactions in living organisms. Calmodulin is a small protein containing 149 amino acids (16.7 kDa). 1991;26(5):2753-8. These negatively charged lipids altered only the velocity of the reactions; the apparent K_m values were not affected. Since this time, the drugs are successfully used for treatment of gastritis, gastric and duodenal ulcer, and gastroesophageal reflux disease. Statins represent a group of compounds that are analogs of mevalonic acid. Biochemistry. 2015;129(2):93-105. Conformational properties of serine proteinase inhibitors (serpins) confer multiple pathophysiological roles. DOI: 10.1016/j.gene.2015.11.052. Submitted: June 7th, 2016 Reviewed: December 13th, 2016 Published: March 29th, 2017 © 2017 The Author(s). The change of serpin conformation leads to the "freezing" of intermediate (complex of enzyme with covalently attached second part of serpin is retained for several days) [21]. The binding is almost irreversible; complex EI does not dissociate even in solution of 6 M urea. 1996;35(7):2437-44. The negatively charged lipids, phosphatidylserine and taurocholate, had differential effects on the hydrolytic rates of the normal and Gaucher disease enzymes from either source. Canonical protein inhibitors of serine proteases. Reversible inhibitors, in turn, may be combined in four groups in accordance with kinetic behavior (competitive, uncompetitive, noncompetitive, and mixed inhibitors) [6]. The mechanism of action of enzyme inhibitors includes a step of enzyme-inhibitor complex formation (EI complex) that has no (or low) enzyme activity. However, the value of maximal velocity (V_{max}) remains constant. 1992;31(9):2582-7. Allosteric regulators often are a final product of whole metabolic pathway that activates enzymes catalyzing a limiting step of the whole pathway. DOI: 10.2174/1570159X11311030006.16. Nelson DL, Cox MM. Cyclic AMP (c-AMP) is allosteric activator of this enzyme. An example of such inhibition is inhibition of acetyl cholinesterase by the excess of acetylcholine [15]. Enzyme inhibition by substrate. Molecular bases for the recognition of short peptide substrates and cysteine-directed modifications of human insulin-degrading enzyme. 1993;30(3):264-9. It means that there is equilibrium between the formation and dissociation of EI complex where k₁ is a constant of the velocity of direct reaction and k₂ is a constant of the velocity of reverse reaction. J Biol Chem. DOI: 10.1016/j.str. Classical example of competitive inhibition is inhibition of fumarate hydratase by malonate which is a substrate analog (Figure 3). Despite the binding maleate to active site, it cannot be converted into the product of reaction. DOI: 10.3389/fendo.2015.00049.25. Hsiao FC, Tung YC, Chou SH, Wu LS, Lin CP, Wang CL, Lin YS, Chang KJ, Chu PH. These K_i values were not influenced by increasing phosphatidylserine or taurocholate concentrations. Availability of ATP or citrate inhibits glycolysis preventing glucose oxidation (negative feedback). In total this effect looks like enzyme activation. This inhibitor binds directly to trypsin active site with K_d value that is equal to 0.1 pM. Sci World J. Membrane interactions of amphiphilic polypeptides mastoparan, melittin, polymyxin B, and cardiotoxin. 2012; 229:15. Colovic MB, Krstić DZ, Lazarević Pašić TD, Bondžić AM, Vasić VM. 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This regulation represents negative and positive feedbacks that slow metabolic pathway when the final product is produced in large amounts or accelerate it when a final product is presented in low concentration. PPIs are introduced in therapeutic practice in 80th years of the twentieth century. For example, magnesium ions interact with ATP or with other nucleotides that are negatively charged molecules, decreasing their charge that provides effective binding of nucleotides in substrate binding site of various enzymes and increasing their activity. In some cases, activation of enzymes is due to the elimination of enzyme inhibitors. 2003;9(11):857-66. Among these drugs are both irreversible and reversible inhibitors that slow down production of prostaglandins that control many aspects of inflammation, smooth muscle contraction, and blood clotting. Methotrexate binds to this enzyme approximately 1000-fold more tightly than the substrate and inhibits nucleotide base synthesis. 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To reveal reactive SH-group in active site of various enzymes, different SH-reagents were used, among them 14C-labeled N-ethylmaleimide, iodoacetate, and iodoacetamide. Binding of two c-AMP molecules to allosteric sites of each regulatory subunit induces their conformation transition that results in dissociation of the tetrameric complex and in activation of catalytic subunits [36]. Inhibitors of ACE are widely used as drugs for treatment of arterial hypertension [25]. Protein pump inhibitors (PPIs). 2007;15(3):1181-205.27. Satoh M, Takahashi Y, Tabuchi T, Minami Y, Tamada M, Takahashi K, Itoh T, Morino Y, Nakamura M. This type of inhibition results in the inability of complex enzyme (E) inhibitor (I) substrate (EIS) to dissociate giving a product of reaction. This enzyme consists of four subunits; two of them are catalytic and two are regulatory. These inhibitors affect also some other viral infections and demonstrated anticancer activity. 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This hypothesis is supported by unsuccessful attempts to create catalytically effective low molecular enzymes having needed active site (molecular mass should be higher than 10,000 Da) or enzyme with correct step of enzymatic reaction has a value of activation energy significantly lower than the value of activation energy for the same chemical reaction, enzymes can increase a rate of reaction 10⁶-10¹⁸ folds. Another well-known irreversible inhibitor is diisopropyl phosphorfluoridate that modifies OH-group of serine residue in active site of such enzymes as chymotrypsin and other serine proteases [10, 11] or acetylcholine esterase in cholinergic synapsis of the nervous system being a potent neurotoxin [12]. Calcium signalling: a historical account, recent developments and future perspectives. Structure. 2005;13:893-904. At high concentrations, two substrate molecules bind in active site the following manner: one substrate molecule binds using the "head" and another molecule using the "tail." This binding is nonproductive and substrate cannot be converted to the product (Figure 2). Front Endocrinol (Lausanne). Mechanisms of action of enzyme activators and some features of allosteric modulators are considered. enzyme conformational mobility classification of enzyme inhibitorsenzyme activators and inhibitorsmechanism of actionEnzymes (E) is a group of biologically active polymers (mainly proteins) that catalyze almost all metabolic reactions in all living organisms. With octyl and dodecyl-β-glucoside nearly normal competitive K_i values were obtained with the splenic enzymes from Gaucher patients. Coupling between catalytic site and collective dynamics: a requirement for mechanochemical activity of enzymes. Statins are used as drugs preventing or slowing the development of atherosclerosis [27]. 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To reveal reactive SH-group in active site of various enzymes, different SH-reagents were used, among them 14C-labeled N-ethylmaleimide, iodoacetate, and iodoacetamide. Binding of two c-AMP molecules to allosteric sites of each regulatory subunit induces their conformation transition that results in dissociation of the tetrameric complex and in activation of catalytic subunits [36]. Inhibitors of ACE are widely used as drugs for treatment of arterial hypertension [25]. Protein pump inhibitors (PPIs). 2007;15(3):1181-205.27. Satoh M, Takahashi Y, Tabuchi T, Minami Y, Tamada M, Takahashi K, Itoh T, Morino Y, Nakamura M. This type of inhibition results in the inability of complex enzyme (E) inhibitor (I) substrate (EIS) to dissociate giving a product of reaction. This enzyme consists of four subunits; two of them are catalytic and two are regulatory. These inhibitors affect also some other viral infections and demonstrated anticancer activity. 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An example of irreversible inhibitor is N-ethylmaleimide that covalently interacts with SH-group of cysteine residues of enzyme molecules, like peptidase (insulin-degrading enzyme) [7]. 3-phosphoglyceraldehyde dehydrogenase [8], or hydrophobic compound from group of cardiotonic steroids that at the last bind to Na,K-ATPase using hydrophobic interactions [9]. And finally, we should note a practical significance of enzyme inhibitors that are a base for the design of different classes of pharmaceutical drugs, pesticides, and insecticides. McAuley M, Timson DJ. Here we present canonical inhibitor classification based on their kinetic behavior and mechanism of action. 2009;106(3):13742-47. Licensee IntechOpen. To stop activation of proteolytic enzymes, the pancreas produces trypsin inhibitor. Different types of reversible inhibition are produced depending on whether these inhibitors bind to the enzyme, the enzyme-substrate complex, or both. 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