

How Do DRUGS Work?

Examples from the PDB archive

PROTEINS are tiny molecular machines that perform most of the tasks needed to keep cells alive. These machines are far too small to see, so you might imagine that it is impossible to affect their action. However, drugs can be used to turn proteins on or off.

DRUGS are small molecules that bind to one specific protein and modify its action. Some very powerful drugs, such as antibiotics or anticancer drugs, are used to completely disable a critical molecular machine. These drugs can kill a bacterial or cancer cell. Other molecules, such as aspirin, gently block less-critical proteins for a few hours. With the use of these drugs, we can make changes inside our own cells, such as the blocking of pain signals. Many structures of drugs that bind to proteins have been determined by scientists. These atomic structures allow us to see how drugs work, and perhaps how to modify them to improve their action. A few examples are shown here. Some of these drugs, like penicillin, were discovered in nature. Other drugs, such as HIV protease inhibitors, were created by using the target protein structure to design new drug molecules. These structures of proteins and drugs, along with many others, can be explored at the RCSB Protein Data Bank (PDB).

1 2 Antibiotics & Antivirals

Antibiotics and antiviral drugs are specific poisons. They need to kill pathogenic organisms like bacteria and viruses without poisoning the patient at the same time. Often, these drugs attack proteins that are only found in the targeted bacterium or virus and which are crucial for their survival or multiplication. For instance, **penicillin** attacks the enzyme that builds bacterial cell walls, and HIV protease inhibitors like **saquinavir** attack an enzyme that is needed for HIV maturation.

1. D-alanyl-D-alanine carboxypeptidase with penicillin (**1pwc**)
2. HIV protease with saquinavir (**1hxb**)

3 4 Anticancer Chemotherapy

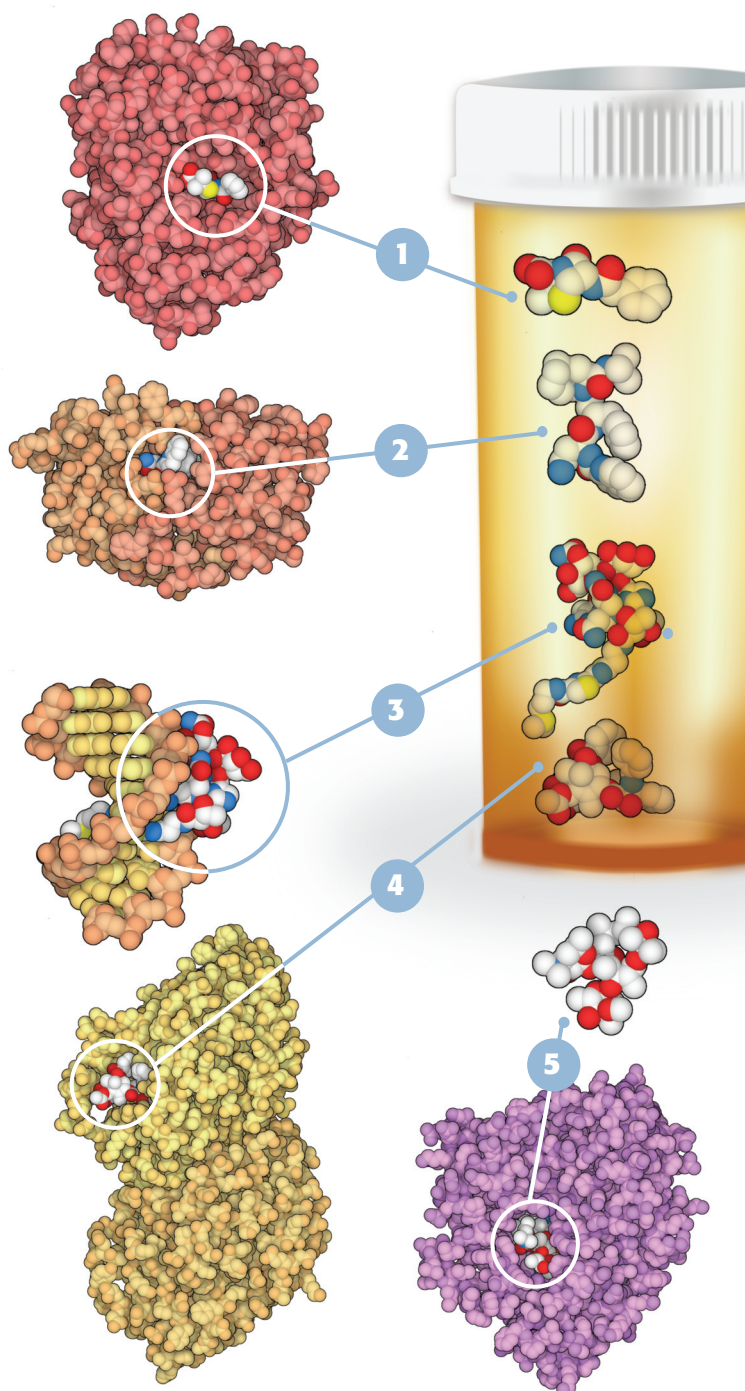
Cancer cells grow and multiply without control. Since these cells are still similar to normal cells, it is difficult to kill them selectively with drugs that can't distinguish between the two. Many drugs currently used for cancer chemotherapy attack all growing cells, including cancer cells and normal cells. This causes the severe side effects of cancer chemotherapy because the drugs attack rapidly-growing cells in hair follicles and the stomach. Two examples are shown here. **Bleomycin** attacks DNA in actively growing cells, often cleaving the DNA chain and killing the cell. **Paclitaxel (Taxol)** binds to tubulin, preventing the action of microtubules during cell division.

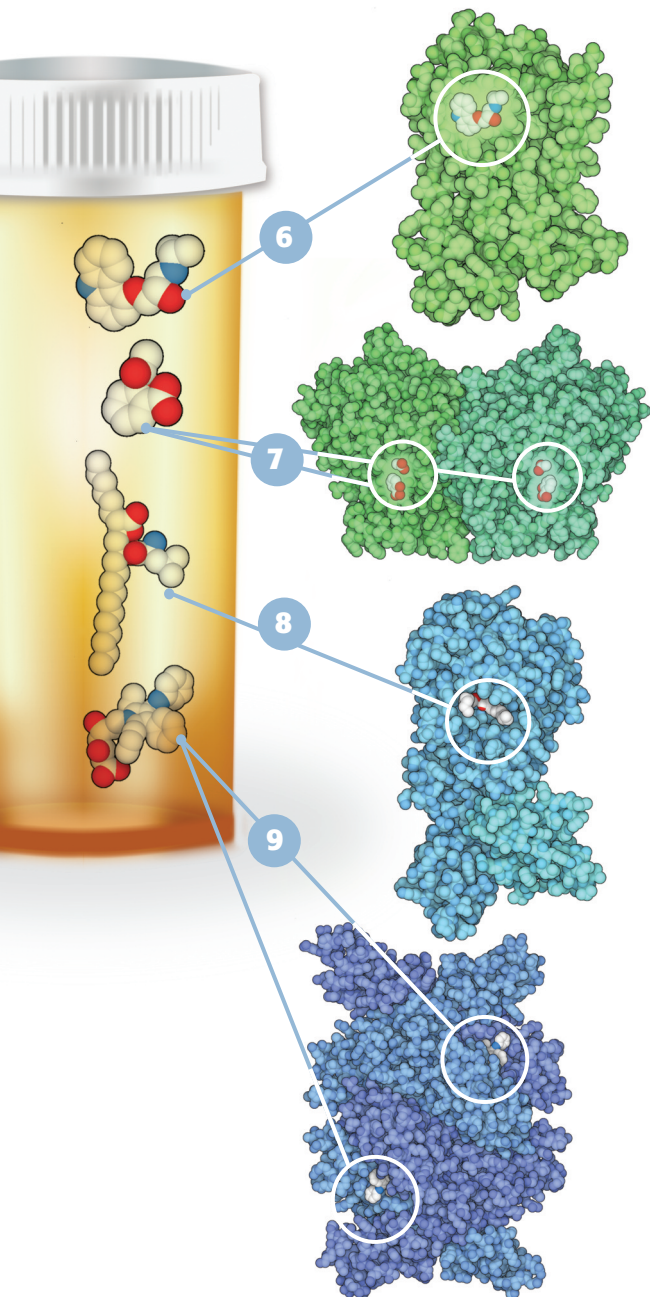
3. DNA with bleomycin (**1mxk**)
4. Tubulin with taxol (**1jff**)

5 Drug Metabolism

You have probably noticed that when you take drugs, the effects gradually wear off in a few hours. Enzymes like cytochrome P450 continually search for drugs and destroy them. This is important because it protects us from poisonous molecules in our diet and in the environment, but it means that we have to take multiple doses of drugs when being treated for a disease.

5. Cytochrome P450 3A4 with erythromycin (**2jod**)





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Drugs of Signaling Proteins

Many drugs are designed to keep bodily processes at normal healthy levels. Much of the body's regulation is done through elaborate communications between cells, so some of the most widely prescribed drugs function by blocking the signaling proteins that allow cells to communicate. G protein-coupled receptors, which transmit signals across cell membranes, are targets for many drugs. For instance, the drug **loratadine (Claritin)** is used to treat allergies because it blocks the histamine receptor; **losartan (Cozaar)** is used to treat high blood pressure because it blocks the angiotensin II receptor; and **carazolol** is one of a large class of beta-blockers that bind to the adrenergic receptor, making it useful for treating heart disease. Signals can also be stopped by blocking the enzymes that create a signaling molecule. **Aspirin** blocks pain at the source by inhibiting the enzyme cyclooxygenase, which makes pain-signaling prostaglandin molecules.

6. Adrenergic receptor with carazolol (**2rh1**)
7. Prostaglandin H2 synthase with aspirin (**1pth**)
The drug breaks into two pieces when it binds to the enzyme, and the smaller piece (an acetyl group) is attached to the enzyme with a covalent bond. The closeup shows the drug in one piece.

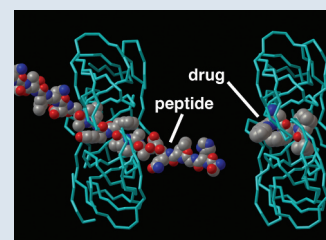
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Lifestyle Drugs

Pharmaceutical scientists have developed a number of drugs that help people modify their own health and bodily function. The drug **orlistat (Xenical or alli)** blocks the action of pancreatic lipase, and thereby reduces the amount of fat that is absorbed from food. **Atorvastatin (Lipitor)** and **simvastatin (Zocor)** lower cholesterol by blocking the action of HMG-CoA reductase, an enzyme involved in the synthesis of cholesterol. These drugs can be used, along with changes in diet and exercise, to help lose weight, regulate cholesterol levels, and control heart disease.

8. Pancreatic lipase with an alkyl phosphonate inhibitor (**1lpb**). The drug orlistat shown on the right is similar to the inhibitor found in the crystal structure.
9. HMG-CoA reductase with atorvastatin (**1hwk**)

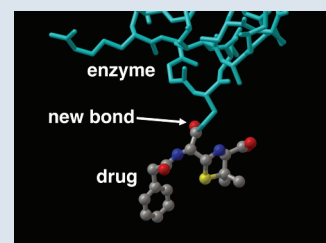
Molecular Mimics



Most drugs mimic the molecules that are normally processed by an enzyme or receptor protein. They bind tightly to the protein and block the site that usually performs the task. For instance, HIV protease normally binds to a protein chain, like the one shown at the left, and clips it into two pieces. Drugs used to treat HIV infection, like saquinavir shown here, are smaller than the protein chain but chemically very similar. The drug binds in a similar position as the peptide, completely blocking the active site so the enzyme is unable to cleave the protein chain. (Image created with the Python Molecular Viewer—mgltools.scripps.edu)

Peptide bound (**2nxd**) and drug bound (**1hxb**) structures of HIV protease.

Suicide Inhibitors



Some drugs are particularly effective because they form a chemical bond to the protein target (shown in turquoise), totally disabling it in the process. Penicillin (shown at the bottom with atomic colors) reacts with a serine amino acid in the bacterial enzyme, forming a new covalent bond to the enzyme. This completely blocks the active site, so the enzyme is unable to perform its role in cell wall synthesis. Another suicide inhibitor, aspirin (shown in #7), attaches an acetyl group to its target which blocks an inflammation pathway.

Penicillin bound structure of D-alanyl-D-alanine carboxypeptidase (PDB entry **1pwc**)

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The structures shown on this poster and their related references can be explored at www.pdb.org.

The RCSB PDB website provides a variety of tools and resources for studying the structures of biological macromolecules and their relationships to sequence, function, and disease.

The RCSB PDB is managed by Rutgers, The State University of New Jersey and the University of California, San Diego, and is a member of the Worldwide Protein Data Bank. It is supported by funds from the National Science Foundation, the National Institute of General Medical Sciences, the Office of Science, Department of Energy, the National Library of Medicine, the National Cancer Institute, National Institute of Neurological Disorders and Stroke, and the National Institute of Diabetes and Digestive and Kidney Diseases.