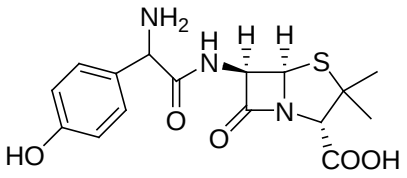
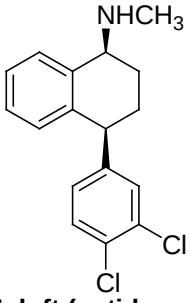
Module 15 Drug Design and Discovery
Lecture 38

15.1 Introduction

Drug is an absorbed substance that changes physical or psychological function in the body. The effect may be beneficial or harmful. Drug may be a gas, liquid or solid and can have a simple or complicated structure. Figure 1 shows examples of widely prescribed drugs.



Trimox (antibiotic)

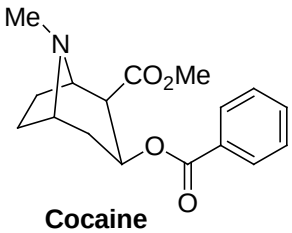


Zoloft (antidepresent)

Figure 1

15.2 Lead Compound

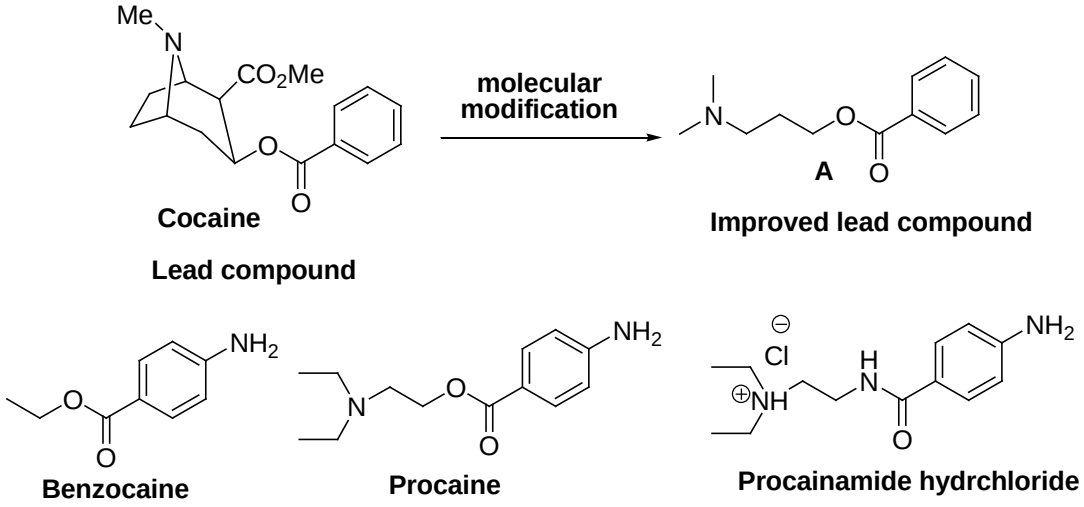
A lead compound is the starting point for designing a new drug. It should have some desirable properties that are likely to be therapeutically useful. For example,



Cocaine

15.3 Molecular Modification

Changing the structure of lead compound is known as **molecular modification**. For example, cocaine is an effective local anesthetic, but it produces disturbing effect on the nervous system that leads to severe depression (Scheme 1). However, the modification of the portion of cocaine structure led to another molecule **A** which exhibit local anesthetic activity without damaging the central nervous system. Based on this several esters have been subsequently synthesized, and benzocaine and procaine have been found to be anesthetic agents. However, procaine was rapidly hydrolyzed by enzymes. Thus, analogue amide derivatives have been further synthesized when procainamide hydrochloride has been found to be effective antiarrhytmic agent.



Scheme 1

15.4 Screening

Screening is a search for a pharmaceutically active compound without having any information about which chemical structure show activity. Some assays can be done in vitro (in glass): for example searching for a compound that will inhibit a particular enzyme. Others are done in vivo- for example, searching for a compound that will save a mouse from a lethal dose of virus. One problem with the viva test is that the drug can be metabolished differently by different animals.

15.5 Receptors

Receptors are proteins that are crucial for the body's communication. They serve as the cell's mail box and receive messages from the chemical messengers and pass them to the target system in the body. The majority of the receptors embedded in the cell membranes, traversing it such that there are extracellular and intracellular regions. In the extracellular there is a hallow which is called binding site. Chemical messenger fit in the binding site and are bound by intermolecular forces in the same way that substrates bound the active sites of the enzyme. Since the process is in equilibrium the messenger does not undergo any reaction and departs unchanged, allowing the receptor to reform its original shape.

For example, see the **G-protein-coupled receptor** (Figure 1). It traverses the cell membrane having the binding site for the chemical messenger in the extracellular region. The second binding site for the G-protein is located in the intracellular region. The intracellular binding site is closed when the receptor is in the resting state.

G-protein is made of three subunits (α,β and γ) and free to move through the cell membrane. G-protein has also binding site for **GDP**.

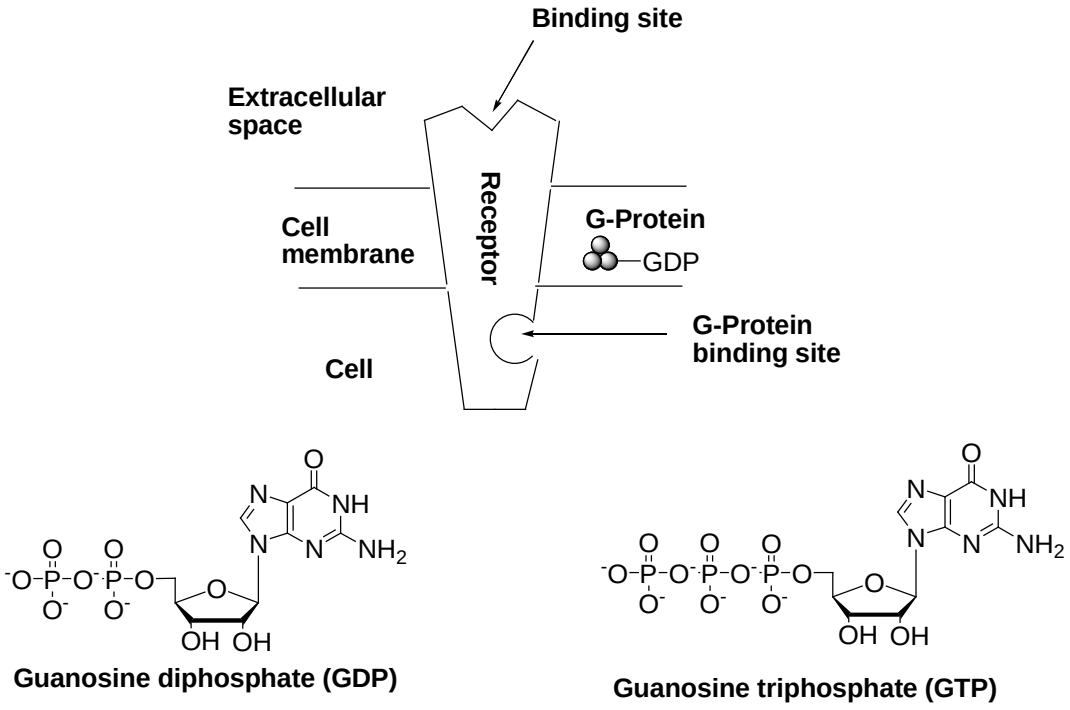


Figure 1

Figure 2 illustrates the involvement of several stages when the receptor conveys the message to the cell.

- A chemical messenger binds to the receptor of the extracellular region.
- The binding site of intracellular region opens up for the binding of G-protein.
- The change in shape of G-protein alters the binding favoring GTP compared to that GDP.
- The binding interaction between the G-protein and GTP causes the G-protein to change in shape again. This changes leads to split of □-subunit from the □ and □ subunits. The splited subunits leave from the binding site of the receptor.

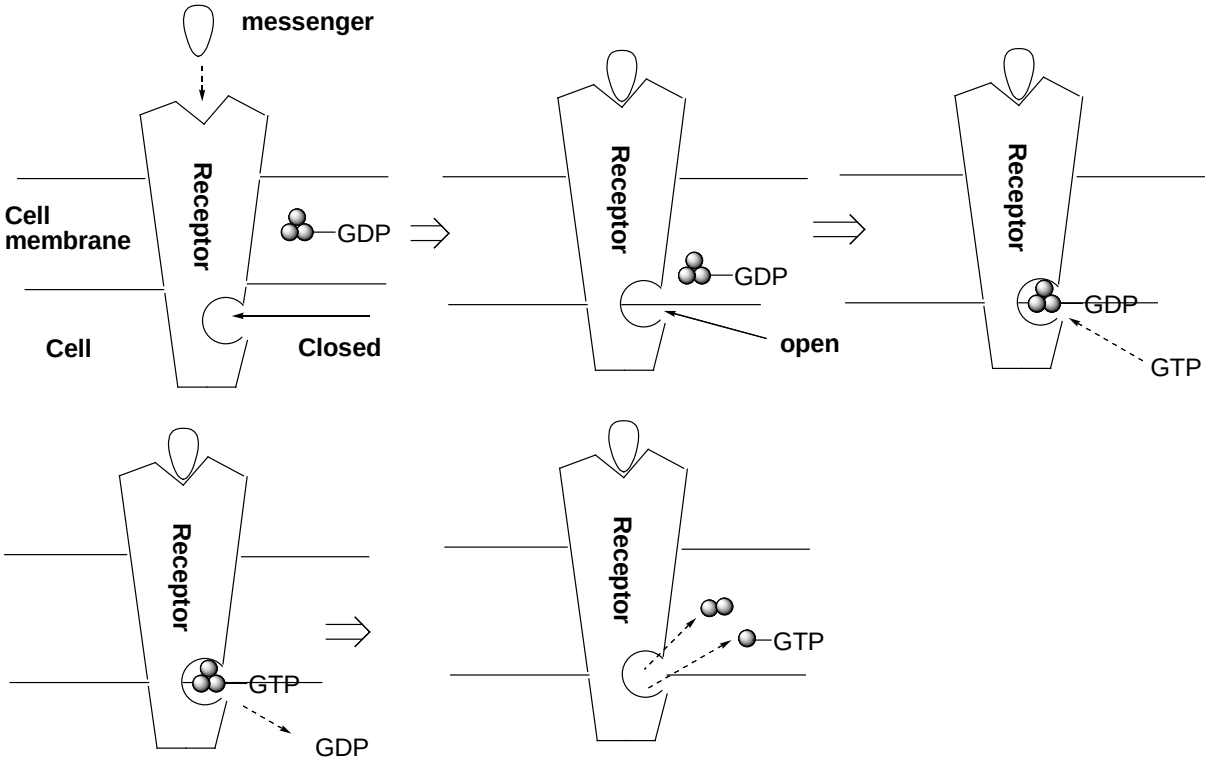


Figure 2

- The α-subunit now can act as a signaling unit. It floats through the membrane until it finds the membrane-bound enzyme is called adeylate cyclase (Figure 3). The enzyme has binding site that can recognize α-subunit and bind it.

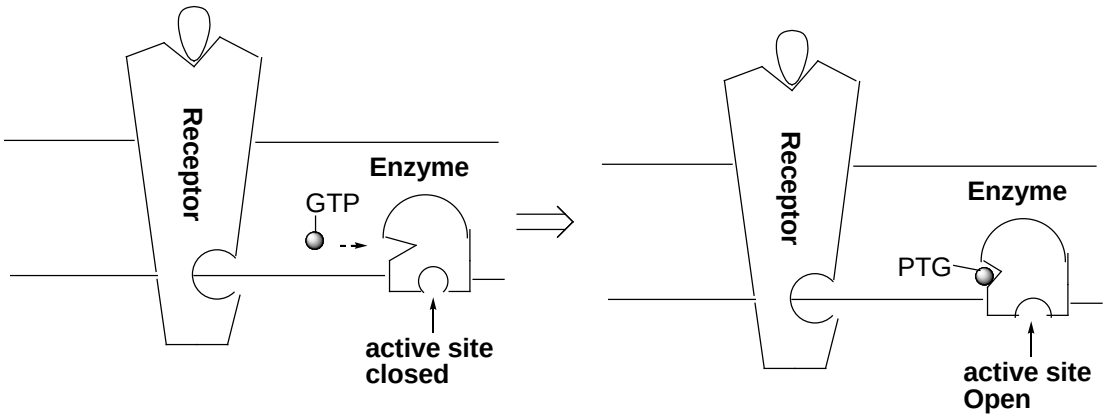
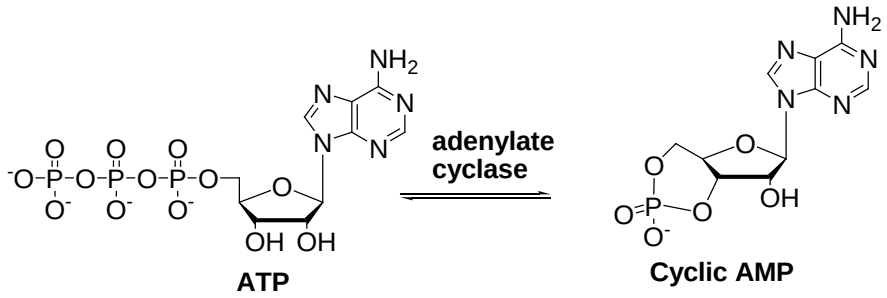


Figure 3

- The resulting induced fit causes the enzyme to change its shape and the active site is opened.
- In the active site ATP binds and cyclise to AMP. This reaction continues as long as the α-subunit is bound in the enzyme.



Scheme 2

15.6 Molecular Modeling

The shape of the molecule is important to be recognized by a receptor. In addition, the compounds having similar structure exhibit similar biological properties. Since computers can draw molecular orbitals on a video display and move them around to assume different conformations, computer ***molecular modeling*** allows more rational drug design. In addition, computer programs allow chemists to scan existing collections of thousands of compounds to find those with the appropriate structural and conformation properties.

15.7 Antiviral Drugs

Few clinically useful drugs have been developed for viral infections. This is because the nature of the virus and they way the replicate fast. Most antiviral drugs are analogues of nucleotides, interfering with DNA or RNA synthesis. Figure 4 shows some of the examples.

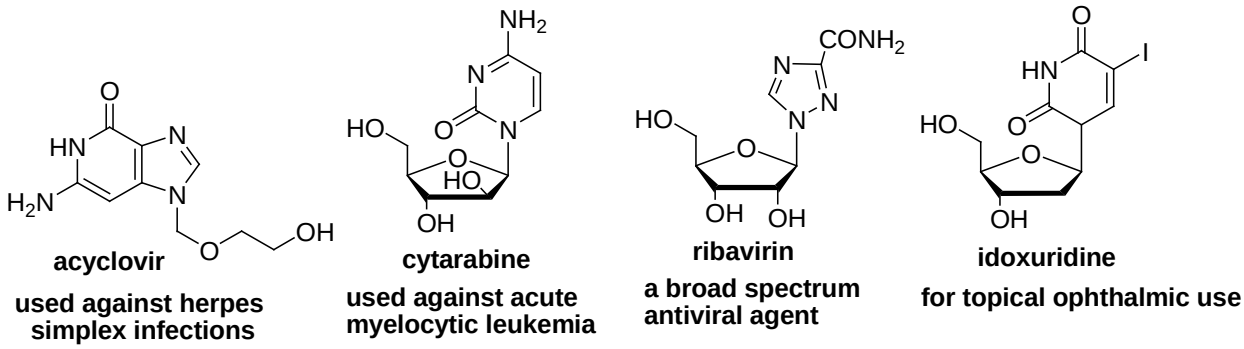


Figure 4