Medicinal Chemistry

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Medicinal and Pharmaceutical Chemistry

References:

1- Wilson and Gisvold's Text book of Organic Medicinal & Pharmaceutical Chemistry, Twelfthe Edition, 2011

2- Gareth Thomas'' Medicinal Chemistry; An Introduction,2nd Edition. 2007.

3- Dr.Iyad Allous lectures

Introduction

- ✓ Medicinal Chemistry: is the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds that can be used as drugs for the prevention, treatment or cure of human and animal diseases.

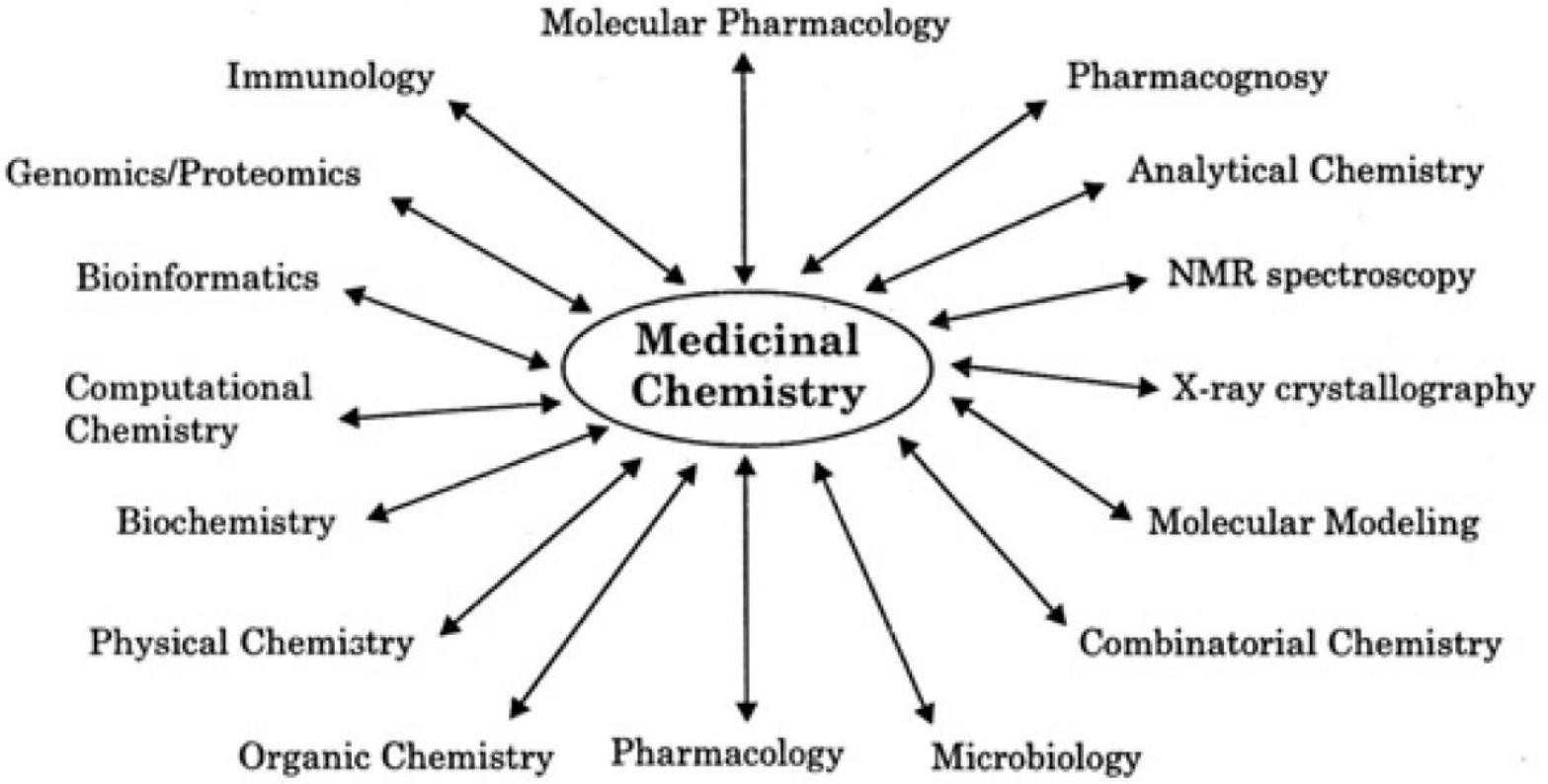
- ✓ Medicinal chemistry includes the study of already existing drugs, of their biological properties and their structure-activity relationships.

- ✓ During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic compounds as drugs.

- ✓ Medicinal chemistry is devoted to the discovery and development of new agents for treating diseases.

Introduction

- ✓ The primary objective of Medicinal Chemistry is the design and discovery of new compounds that are suitable for use as drugs.
- ✓ This process involves a team of workers from a wide range of disciplines such as chemistry, biology, biochemistry, pharmacology, mathematics, medicine and computing, amongst others



Introduction

Medicinal chemistry covers the following stages:

I. The first stage is lead discovery in which new active substances or drugs are identified and prepared from natural sources, organic chemical reactions or biotechnological processes.

II. The second stage is optimization of lead structure to improve potency, selectivity and to reduce toxicity.

III. The third stage is development stage, which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it clinically

Drugs and drug targets an overview

✓ What is a Drug ?

Drugs are defined as chemical substances that are used to prevention, treatment or cure of human, animal, and plant.

✓ Why we need to design and discovery of new drugs?

New drugs are constantly required for:

1.treatment of newly identified diseases.

2.improving the treatment of existing diseases.

3.combat drug resistance.

4.production of safer drugs by the reduction or removal of adverse side effects

Drugs and drug targets an overview

- Drug Resistance occurs when a drug is no longer effective in controlling a medical condition.
- Tolerance is a situation where higher levels of a drug are required to get the same biological response.

✓ Drug Resistance arises in people for a variety of reasons:

1. development of an enzyme that metabolises the drug.

2. downregulation of receptors (repeated stimulation of a receptor results in the receptor being broken down).

3. appearance of a drug-resistant strains of microorganisms.

Drugs & Drug Targets

- The main molecular targets for drugs are:

1. proteins (enzymes, receptors, and transport proteins).
2. nucleic acids (DNA and RNA).

✓ The interaction of a drug with a macromolecular target involves a process known as Binding.

✓ a specific area of the macromolecule where Binding takes place known as the Binding Site.

✓ Typically, this takes the form of a hollow or canyon on the surface of the macromolecule allowing the drug to sink into the body of the larger molecule.

Drugs & Drug Targets

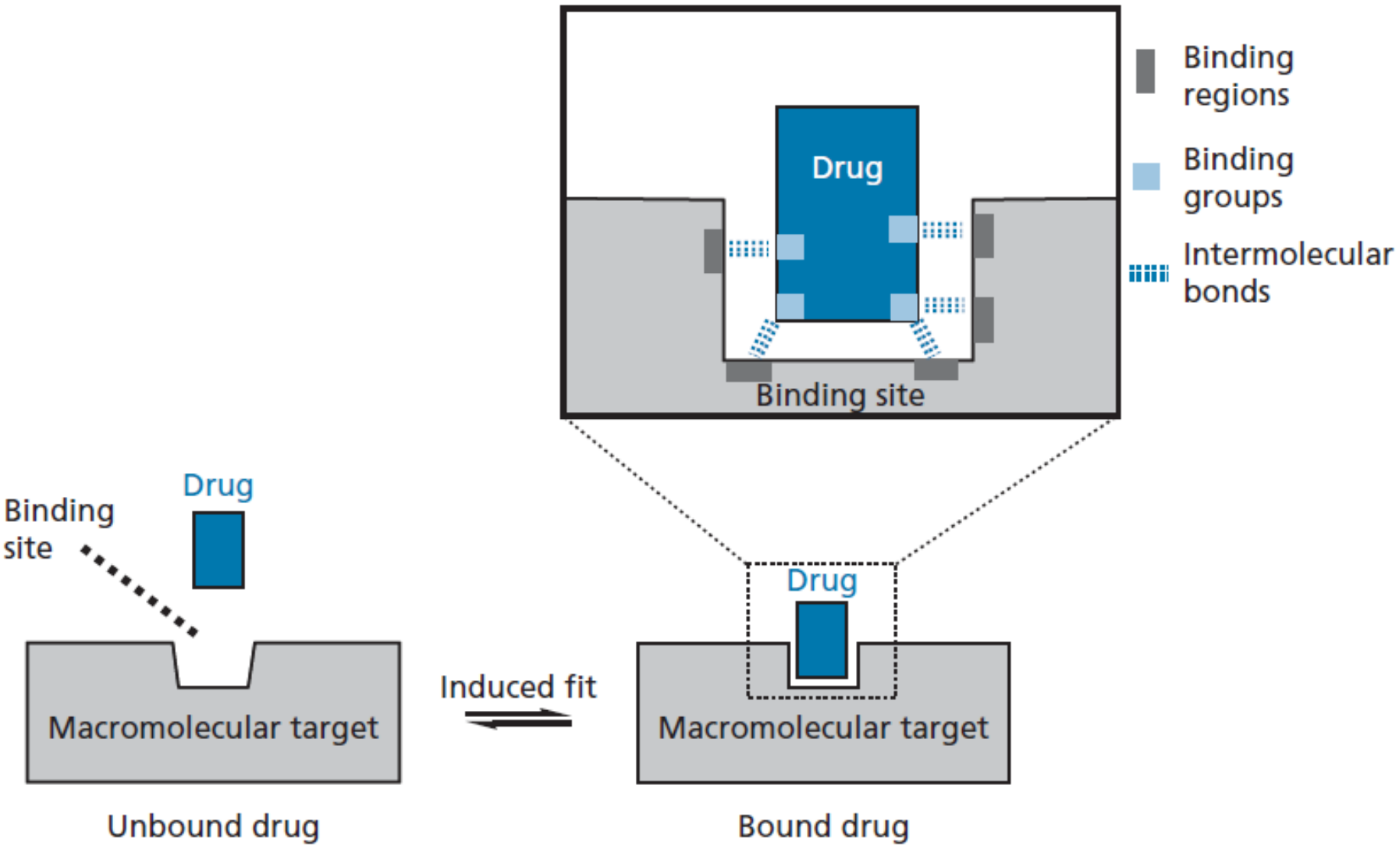
- Some drugs react with the binding site and become permanently attached via a Covalent Bond that has a bond strength of 200–400 kJ/mol.
- Most drugs interact through weaker forms of interaction known as Intermolecular Bonds.
- Intermolecular Bonds include:

1. Ionic Bonds.
2. Hydrogen Bonds.
3. Van Der Waals Interactions.
4. Dipole–dipole Interactions.
5. Ion-dipole interaction.
6. Hydrophobic Interactions.

Drugs & Drug Targets

- ✓ The Functional groups of the drug which can be important in forming intermolecular bonds with the target binding site, are called Binding Groups.
- ✓ However, the carbon skeleton of the drug also plays an important role in binding the drug to its target through van der Waals interactions.
- ✓ The specific regions of the target binding site where the binding takes place are known as Binding Regions.
- ✓ The study of how drugs interact with their targets through binding interactions and produce a pharmacological effect is known as Pharmacodynamics.

Drugs & Drug Targets

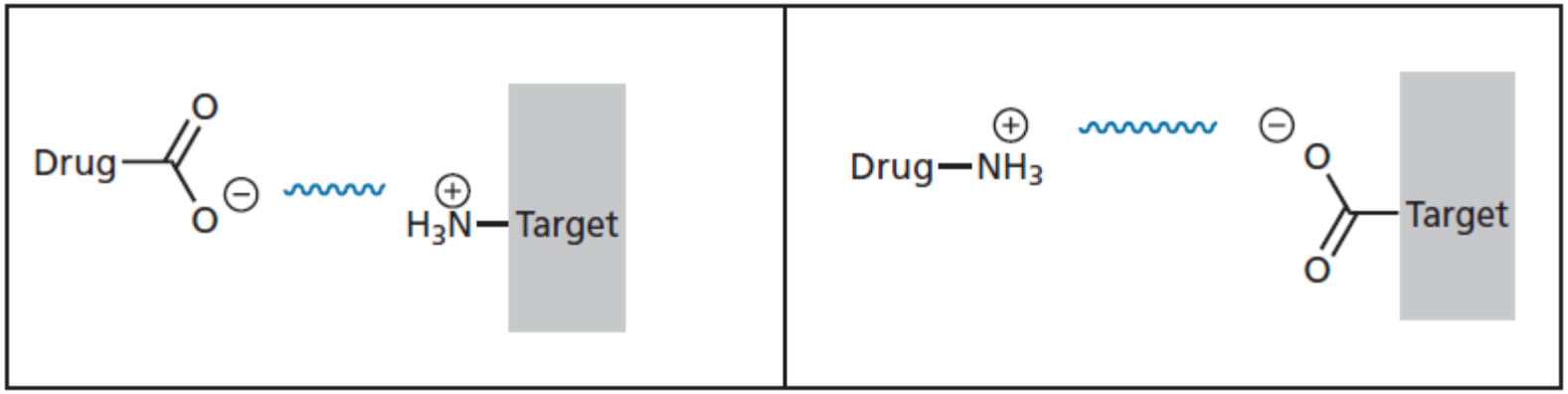


intermolecular bonding interactions

- ✓ There are several types of intermolecular bonding interactions, which differ in their bond strengths:

1. Electrostatic or Ionic bonds:

An ionic or electrostatic bond is the strongest of the intermolecular bonds (20–40 kJ mol^{-1}) and takes place between groups that have opposite charges, such as a carboxylate ion and an aminium ion.



intermolecular bonding interactions

2. Hydrogen bond:

A hydrogen bond takes place between an electron-rich heteroatom and an electron-deficient hydrogen.

- ✓ The electron-rich heteroatom has to have a lone pair of electrons and is usually oxygen or nitrogen.
- ✓ The electron-deficient hydrogen is usually linked by a covalent bond to an electronegative atom, such as oxygen or nitrogen.
- ✓ The strength of a hydrogen bond can vary widely varying from 16 to 60 kJ mol^{-1} .

intermolecular bonding interactions

2. Hydrogen bond

- ✓ The functional group that provides the hydrogen for the hydrogen bond known as a Hydrogen Bond Donor HBD.
- ✓ The functional group that provides the electron-rich atom to receive the hydrogen bond is known as a Hydrogen Bond Acceptor HBA.

Hydrogen bonding shown by a dashed line between a drug and a binding site (X, Y = oxygen or nitrogen; HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

intermolecular bonding interactions

2. Hydrogen bond

- ✓ Some functional groups can act both as hydrogen bond donors and hydrogen bond acceptors (e.g. OH, NH_2).

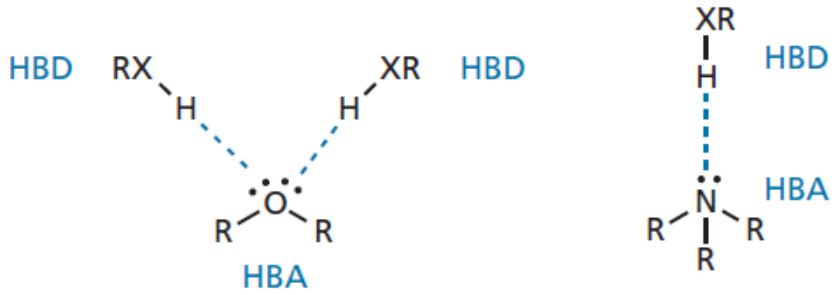


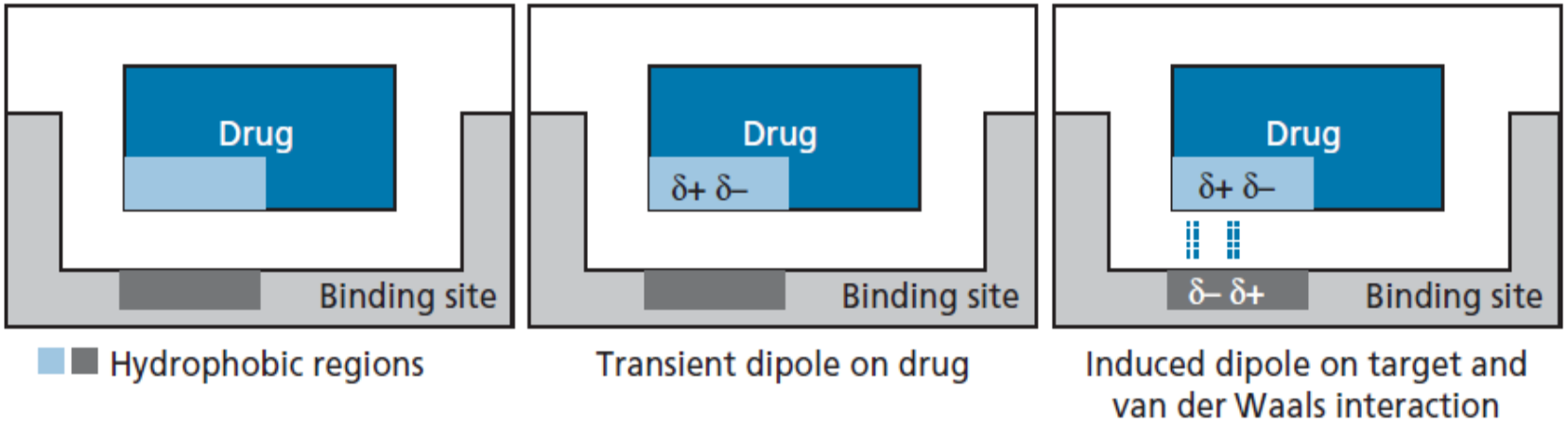
FIGURE 1.9 Oxygen and nitrogen acting as hydrogen bond acceptors (HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

- ✓ When such a group is present in a binding site, it is possible that it might bind to one ligand as a hydrogen bond donor and to another as a hydrogen bond acceptor.
- ✓ This characteristic is given the term hydrogen bond Flip-Flop.

intermolecular bonding interactions

3. Van der Waals interactions

Van der Waals interactions involve interactions between hydrophobic regions of different molecules, such as aliphatic substituents or the overall carbon skeleton.



intermolecular bonding interactions

4. Dipole-dipole interactions

- ✓ Many molecules have a permanent dipole moment resulting from the different electronegativities of the atoms and functional groups present.

- ✓ For example, a ketone has a dipole moment due to the different electronegativities of the carbon and oxygen making up the carbonyl bond.

- ✓ The binding site also contains functional groups, so it is inevitable that it too will have various local dipole moments.

intermolecular bonding interactions

4. Dipole-dipole interactions

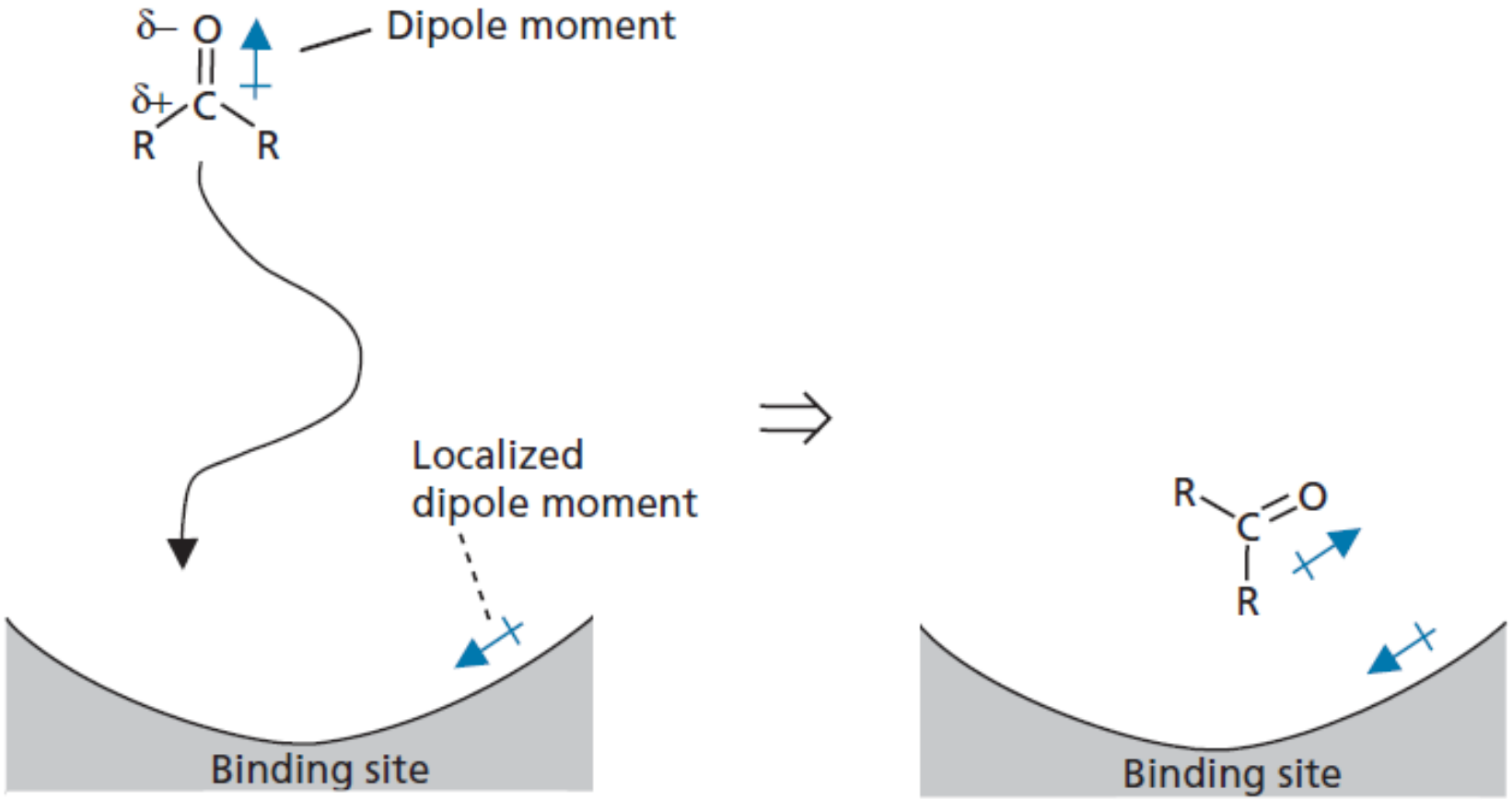


FIGURE 1.15 Dipole–dipole interactions between a drug and a binding site.

intermolecular bonding interactions

5. Ion-dipole interactions

- ✓ An ion-dipole interaction is where a charged or ionic group in one molecule interacts with a dipole in a second molecule.

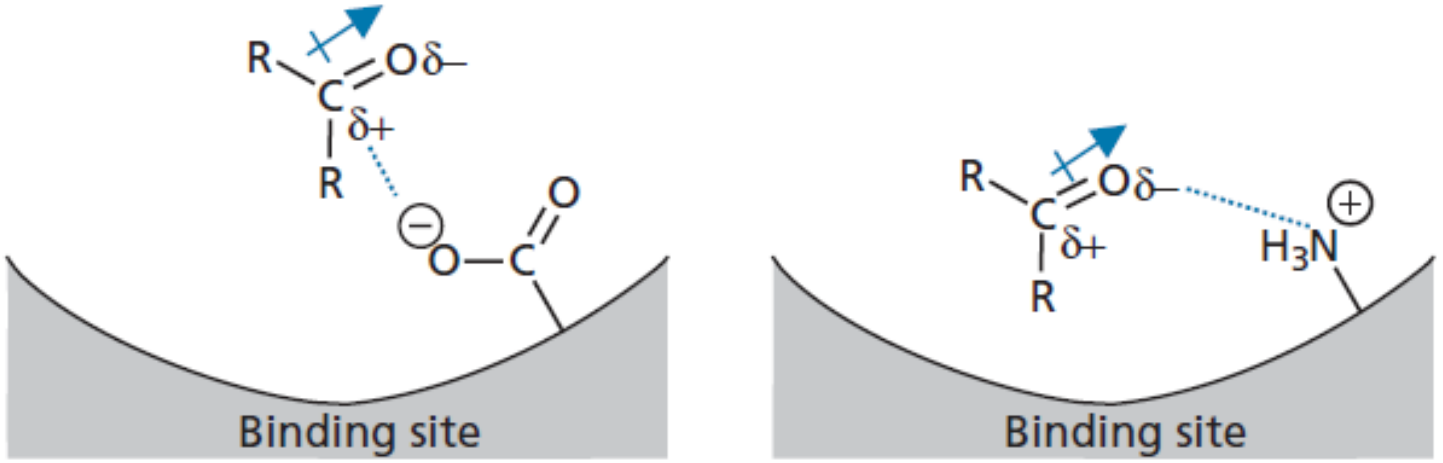


FIGURE 1.16 Ion–dipole interactions between a drug and a binding site.

intermolecular bonding interactions

5. Ion-dipole interactions

- ✓ Interactions involving an induced dipole moment have been proposed.
- ✓ There is evidence that an aromatic ring can interact with an ionic group such as a quaternary ammonium ion.

- ✓ induced dipole moment interaction is feasible if the positive charge of the quaternary ammonium group distorts the π electron cloud of the aromatic ring to produce a dipole moment where the face of the aromatic ring is electron-rich and the edges are electron-deficient.
- ✓ This is also called a cation-pi interaction.

intermolecular bonding interactions

5. Ion-dipole interactions

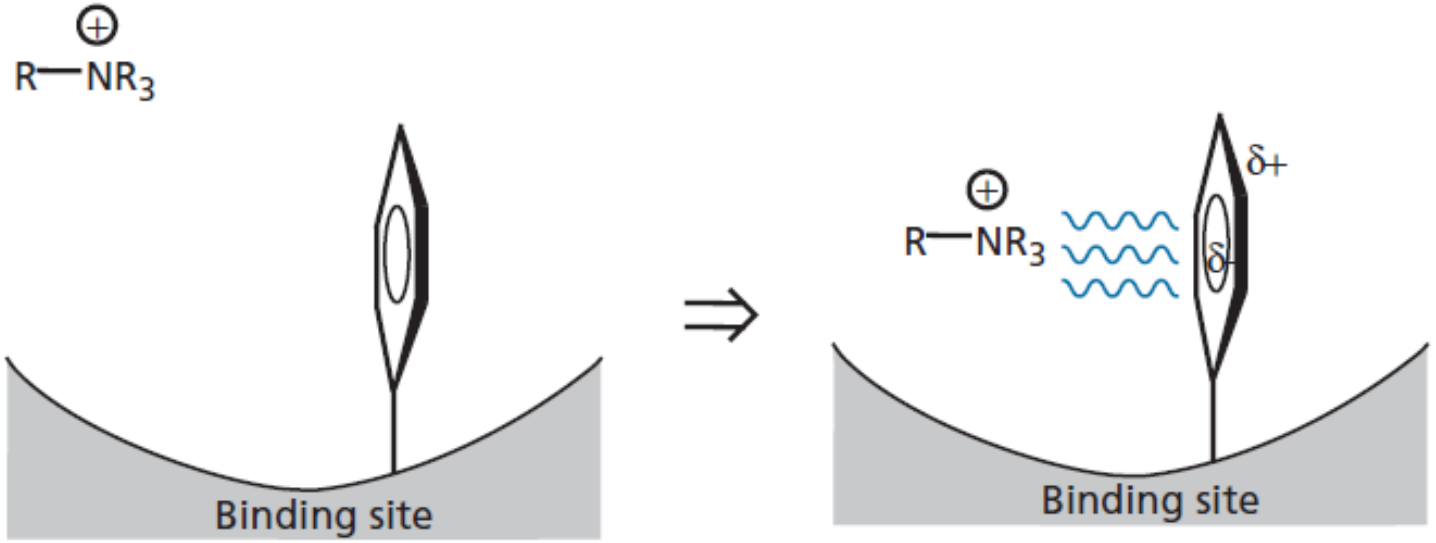


FIGURE 1.17 Induced dipole interaction between an alkylammonium ion and an aromatic ring.

intermolecular bonding interactions

6. Hydrophobic interactions

- ✓ It is not possible for water to solvate the non-polar or hydrophobic regions of a drug or its target binding site.
- ✓ Instead, the surrounding water molecules form stronger than-usual interactions with each other, resulting in a more ordered layer of water next to the non-polar surface.
- ✓ When the hydrophobic region of a drug interacts with a hydrophobic region of a binding site, these water molecules are freed and become less ordered.
- ✓ This leads to an increase in entropy and a gain in binding energy.

intermolecular bonding interactions

6. Hydrophobic interactions

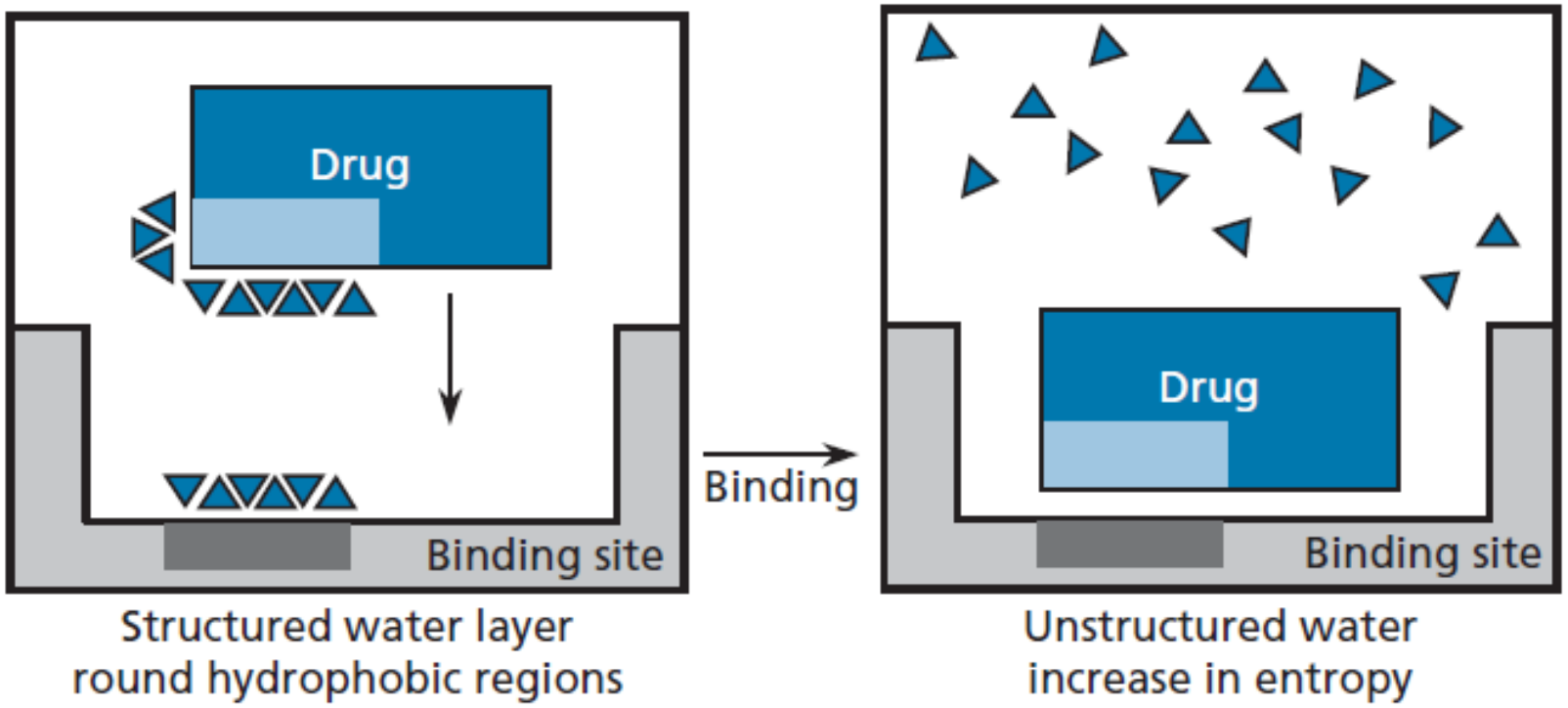


FIGURE 1.19 Hydrophobic interactions.

Classification of Drugs

- ✓ There are four main ways in which drugs might be classified or grouped:

1. Pharmacological Effect

- ✓ Drugs can be classified depending on the biological or pharmacological effect that they have, for example analgesics, antipsychotics, antihypertensives, anti-asthmatics, and antibiotics.
- ✓ This is useful if one wishes to know the full scope of drugs available for a certain ailment, but it means that the drugs included are numerous and highly varied in structure.

Classification of Drugs

2. Chemical Structure

- ✓ Many drugs which have a common skeleton are grouped together, for example penicillins, barbiturates, opiates, steroids, and catecholamines.

- ✓ In some cases, this is a useful classification as the biological activity and mechanism of action is the same for the structures involved, for example the antibiotic activity of penicillins.

- ✓ However, not all compounds with similar chemical structures have the same biological action. For example, steroids share a similar tetracyclic structure, but they have very different effects in the body.

Classification of Drugs

3. Target System

- ✓ Drugs can be classified according to whether they affect a certain target system in the body.
- ✓ An example of a target system is where a neurotransmitter is synthesized, released from its neuron, interacts with a protein target, and is either metabolized or reabsorbed into the neuron.
- ✓ For example the drugs that affect the cholinergic and the adrenergic system

4. Target Molecule

- ✓ Some drugs are classified according to the molecular target with which they interact.
- ✓ For example, anticholinesterases are drugs which act by inhibiting the enzyme acetylcholinesterase .

Drug Discovery, Design, and Development

we can identify the following stages in drug discovery, design and development:

1.Drug discovery: finding a lead compound

- ✓Choose a disease
- ✓Choose a drug target
- ✓Identify a bioassay
- ✓Find a lead compound
- ✓Isolate and purify the lead compound if necessary
- ✓Determine the structure of the lead compound.

Drug Discovery, Design, and Development

2. Drug design

- ✓ Identify structure–activity relationships (SARs)
- ✓ Identify the pharmacophore
- ✓ Improve target interactions (pharmacodynamics)
- ✓ Improve pharmacokinetic properties

Drug Discovery, Design, and Development

3. Drug development

- ✓ Patent the drug
- ✓ Carry out preclinical trials (drug metabolism, toxicology, formulation and stability tests, pharmacology studies, etc.)
- ✓ Design a manufacturing process (chemical and process development)
- ✓ Carry out clinical trials
- ✓ Register and market the drug
- ✓ Make money!

Drug discovery: finding a lead compound

- ✓ Once a target and a testing system have been chosen, the next stage is to find a lead compound

Lead compound :

- ✓ is a compound which shows the desired pharmacological activity.
- ✓ The level of activity may not be very great and there may be undesirable side effects, but the lead compound provides a starting point for the drug design and development process.

Drug discovery: finding a lead compound

✓ There are various ways for finding a lead compound :

1. Screening of natural products
2. Medical folklore
3. Screening synthetic compound ‘libraries’
4. Existing drugs
5. Starting from the natural ligand or modulator
6. Combinatorial and parallel synthesis
7. Computer-aided design of lead compounds
8. Serendipity and the prepared mind
9. Computerized searching of structural databases
10. Fragment-based lead discovery

Drug discovery: finding a lead compound

1. Screening of natural products:

- ✓ Natural products are a rich source of biologically active compounds.
- ✓ Many of today's medicines are either obtained directly from a natural source or were developed from a lead compound originally obtained from a natural source.

- ✓ Usually, the natural source has some form of biological activity, and the compound responsible for that activity is known as the active principle.
- ✓ Most biologically active natural products are secondary metabolites with quite complex structures and several chiral centres.

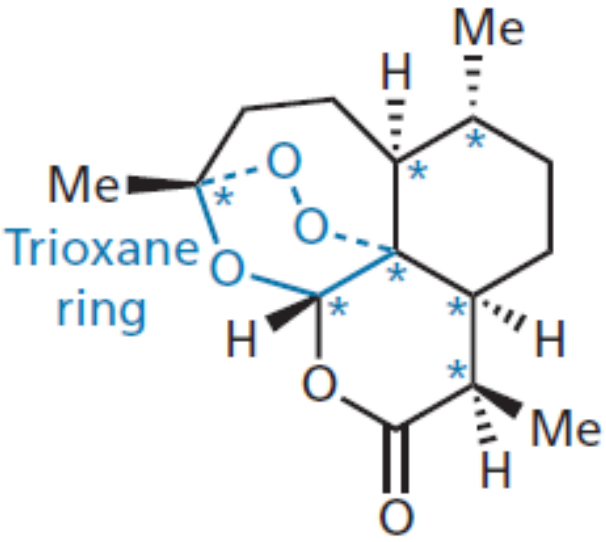
Drug discovery: finding a lead compound

1. Screening of natural products:

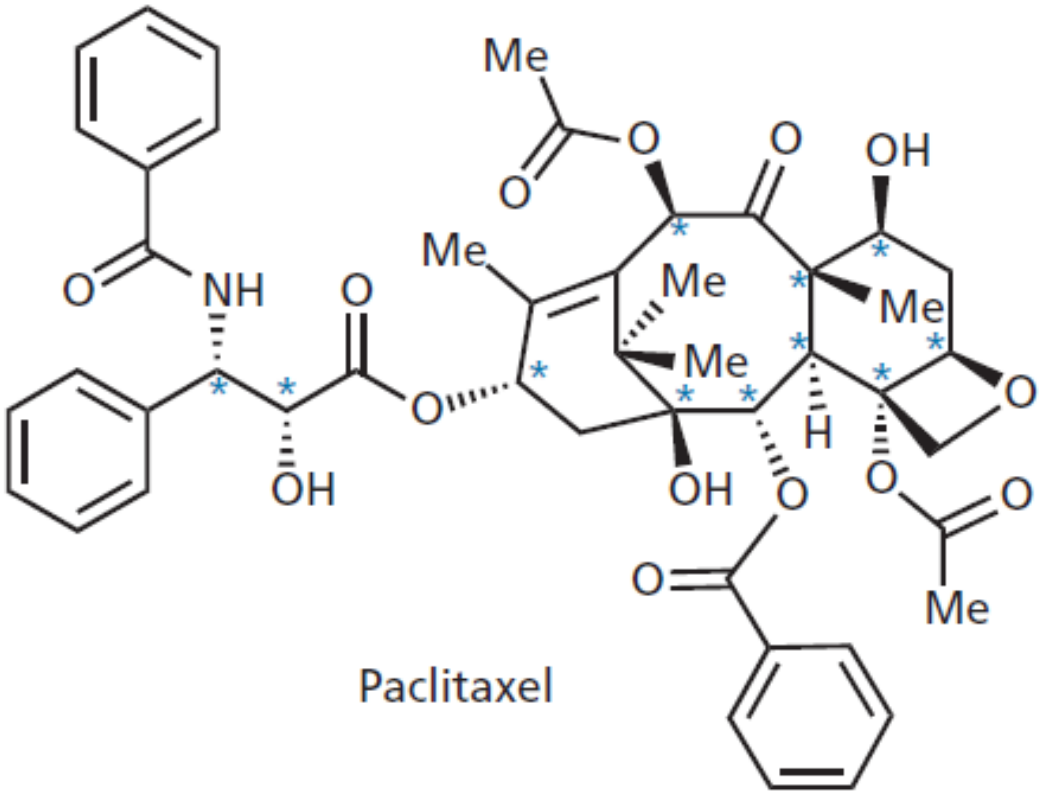
- ✓ This has an advantage in that they are extremely novel compounds.
- ✓ Unfortunately, this complexity also makes their synthesis difficult and the compounds usually have to be extracted from their natural source (which is a slow, expensive, and inefficient process).
- ✓ As a result, there is usually an advantage in designing simpler analogues.
- ✓ Many natural products have radically new chemical structures which no chemist would dream of synthesizing. For example, the antimalarial drug Artemisinin

Drug discovery: finding a lead compound

1. Screening of natural products:



Artemisinin



Paclitaxel

Drug discovery: finding a lead compound

1. Screening of natural products:

- The Plant Kingdom

- ✓ Plants have always been a rich source of lead compounds (e.g. morphine, cocaine, digitalis, quinine, tubocurarine, nicotine, and muscarine).

- ✓ Many of these lead compounds are useful drugs in themselves (e.g. morphine and quinine), and others have been the basis for synthetic drugs (e.g. local anaesthetics developed from cocaine).

- ✓ Plants still remain a promising source of new drugs and will continue to be so.

Drug discovery: finding a lead compound

1. Screening of natural products:

- ✓ The Plant Kingdom
- ✓ Plants provide a bank of rich, complex, and highly varied structures which are unlikely to be discovered from other sources.
- ✓ The rainforests of the world are particularly rich in plant species which have still to be discovered, let alone studied.
- ✓ Who knows how many exciting new lead compounds await discovery for the fight against cancer, AIDS, or any of the other myriad of human afflictions?
- ✓ This is one reason why the destruction of rainforests and other ecosystems is so tragic; once these ecosystems are destroyed, unique plant species are lost to medicine for ever.

Drug discovery: finding a lead compound

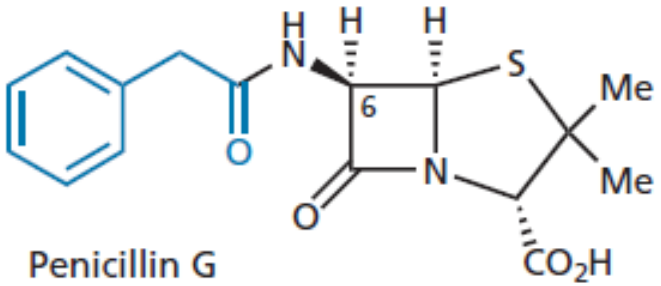
1. Screening of natural products:

- ✓ Microorganisms
- ✓ Microorganisms such as bacteria and fungi have also provided rich pickings for drugs and lead compounds.
- ✓ These organisms produce a large variety of antimicrobial agents which have evolved to give their hosts an advantage over their competitors in the microbiological world.
- ✓ The screening of microorganisms became highly popular after the discovery of penicillin.
- ✓ Soil and water samples were collected from all round the world in order to study new fungal or bacterial strains, leading to an impressive arsenal of antibacterial agents, such as the Cephalosporins, Tetracyclines, Aminoglycosides, Rifamycins, Chloramphenicol, Vancomycin.

Drug discovery: finding a lead compound

1. Screening of natural products:

✓ Microorganisms



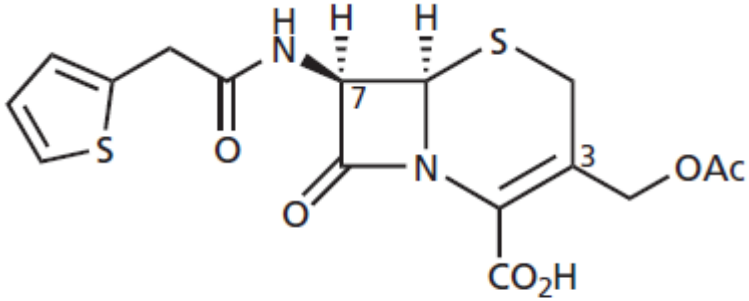
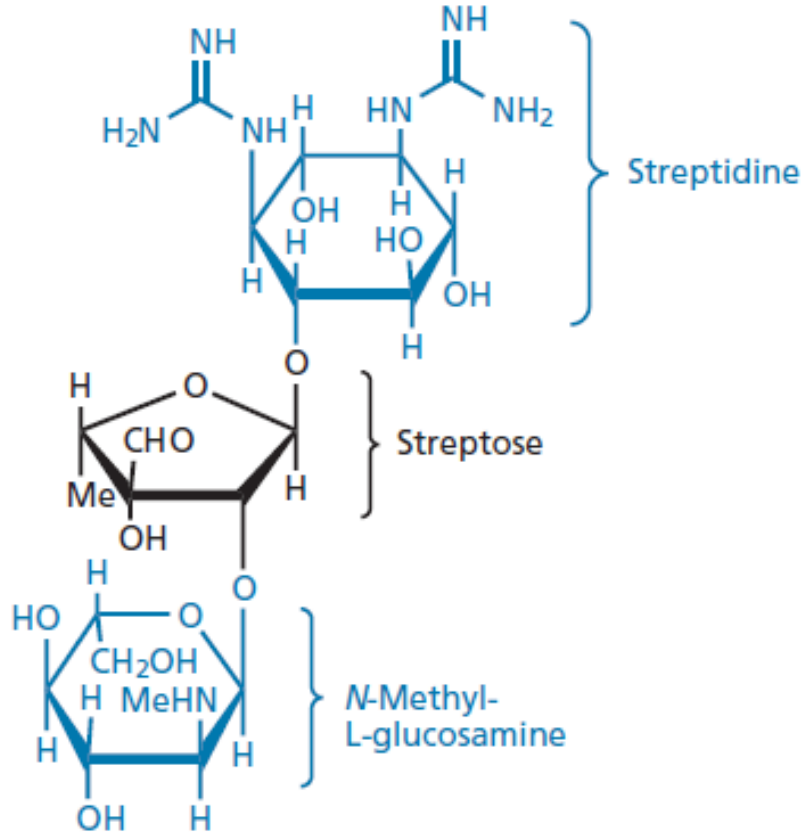


FIGURE 19.39 Cephalothin.



Streptomycin (from *Streptomyces griseus*)

Drug discovery: finding a lead compound

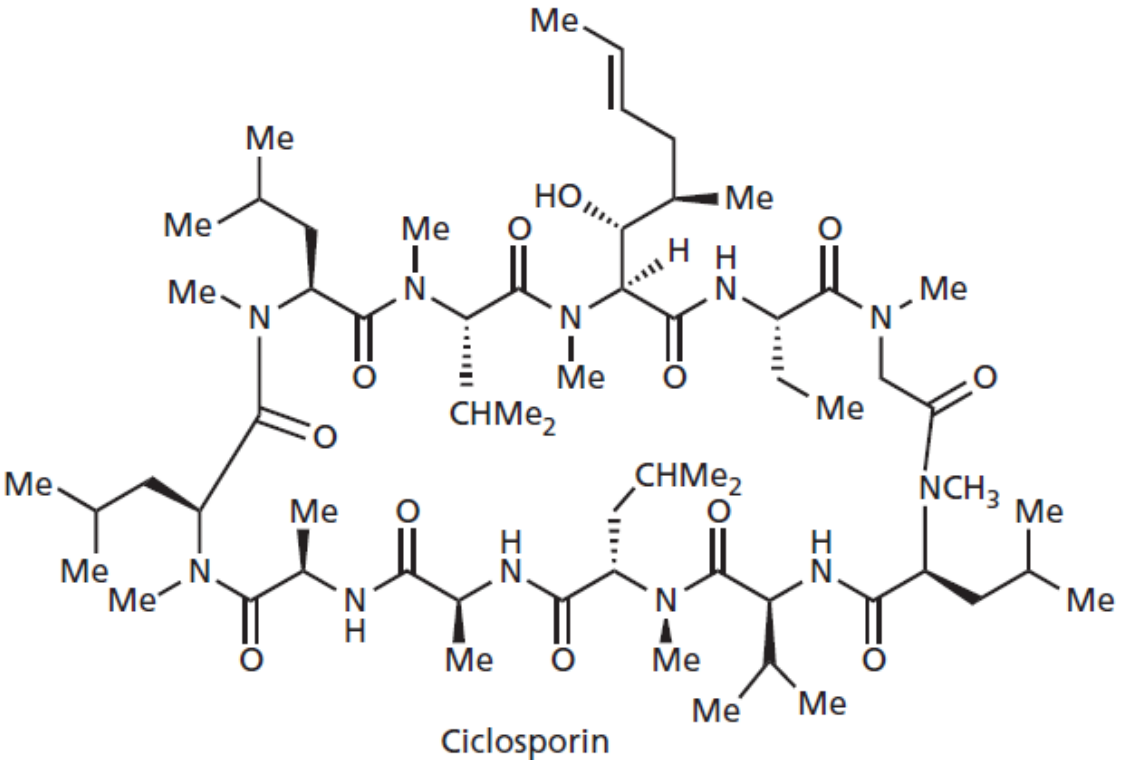
1. Screening of natural products:

- ✓ Microorganisms
- ✓ Although most of the drugs derived from microorganisms are used in antibacterial therapy, some microbial metabolites have provided lead compounds in other fields of medicine.
- ✓ For example the fungal metabolite Lovastatin which was the first of the clinically useful statins found to lower cholesterol levels
- ✓ another fungal metabolite called Ciclosporin, which is used to suppress the immune response after organ transplants
- ✓ Lipstatin is a natural product which was isolated from Streptomyces toxytricini. It inhibits pancreatic lipase and was the lead compound for the anti-obesity compound Orlistat

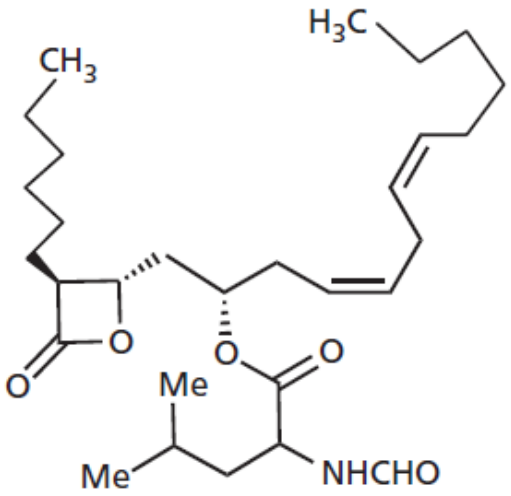
Drug discovery: finding a lead compound

1. Screening of natural products:

✓ Microorganisms



Ciclosporin



Lipstatin

Drug discovery: finding a lead compound

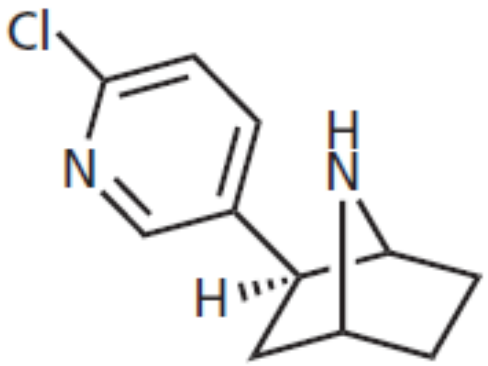
1. Screening of natural products:

- ✓ Marine sources
- ✓ In recent years, there has been great interest in finding lead compounds from marine sources.
- ✓ Coral, sponges, fish, and marine microorganisms have a wealth of biologically potent chemicals with interesting anti inflammatory, antiviral, and anticancer activity.
- ✓ For example, Curacin A is obtained from a marine bacterium, and shows potent antitumour activity.
- ✓ Other antitumour agents derived from marine sources include bryostatins , Dolastatins , Cephalostatins ,Halichondrin B.

Drug discovery: finding a lead compound

1. Screening of natural products:

- ✓ Animals sources
- ✓ Animals can sometimes be a source of new lead compounds.
- ✓ For example is a potent analgesic Epibatidine obtained from the skin extracts of the Ecuadorian poison frog.



Epibatidine

Drug discovery: finding a lead compound

1. Screening of natural products:

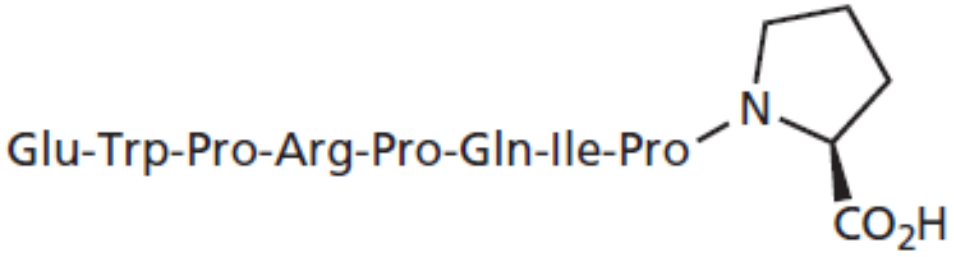
- ✓ Venoms and toxins
- ✓ Venoms and toxins from animals, plants, snakes, spiders, scorpions, insects, and microorganisms are extremely potent because they often have very specific interactions with a macromolecular target in the body.

- ✓ Venoms and toxins have been used as lead compounds in the development of novel drugs.
- ✓ For example, Teprotide , a peptide isolated from the venom of the Brazilian viper, was a lead compound for the development of the antihypertensive agents Cilazapril and Captopril

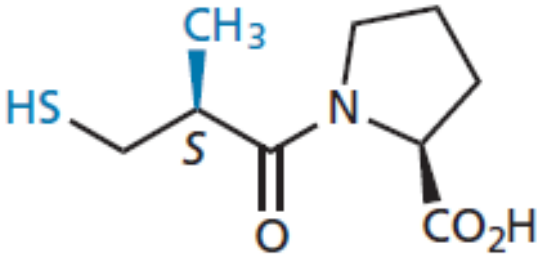
Drug discovery: finding a lead compound

1. Screening of natural products:

✓ Venoms and toxins



Teprotide; IC_{50} 0.9 μM



Captopril; IC_{50} 23 nM

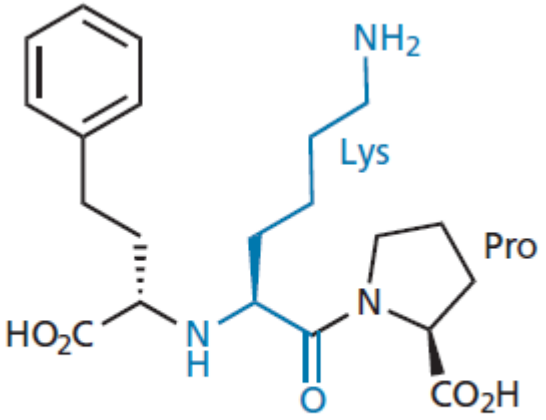


FIGURE CS2.11 Lisinopril.

Drug discovery: finding a lead compound

2. Medical folklore:

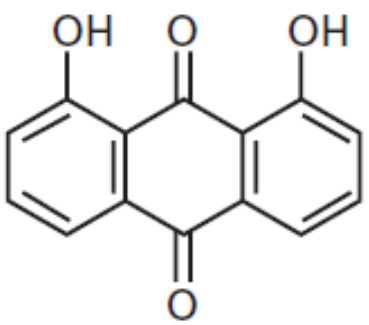
- ✓ The most significant chemicals in rhubarb root are anthraquinones, which were used as the lead compounds in the design of the laxative dantron.

- ✓ The ancient records of Chinese medicine also provided the clue to the novel antimalarial drug artemisinin.

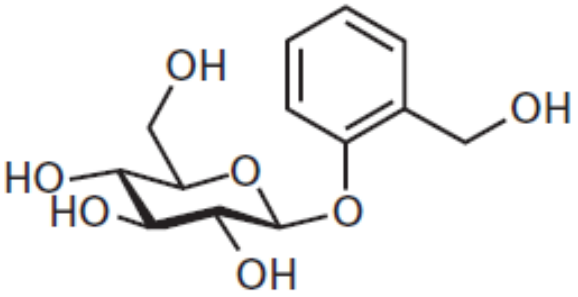
- ✓ The therapeutic properties of the opium poppy (active principle Morphine) were known in Ancient Egypt, as were those of the Solanaceae plants in ancient Greece (active principles atropine and hyoscine).
- ✓ The herbalists in medieval England used extracts from the willow tree (active principle Salicin)

Drug discovery: finding a lead compound

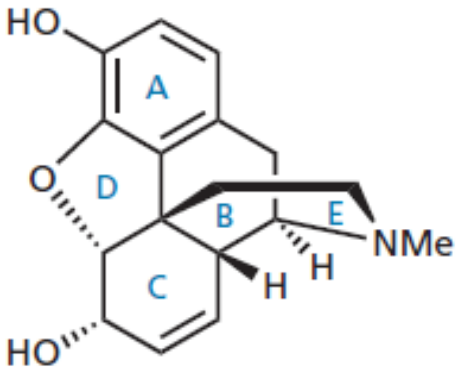
2. Medical folklore:

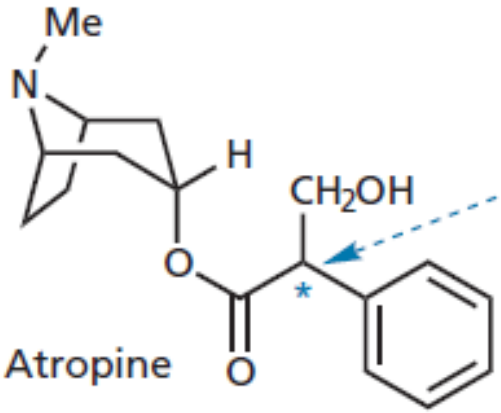


Dantron



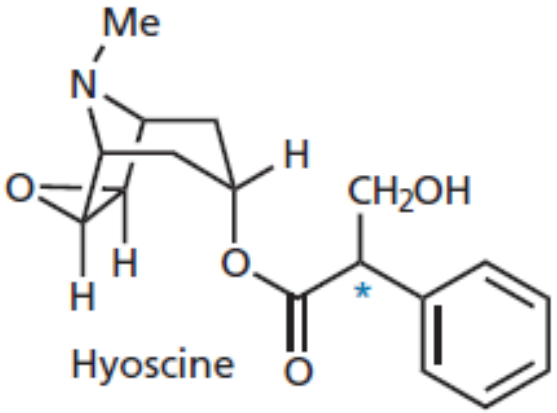
Salicin





Atropine

Easily racemized



Hyoscine

Drug discovery: finding a lead compound

3. Screening synthetic compound ‘libraries’:

- ✓ The thousands of compounds which have been synthesized by the pharmaceutical companies over the years are another source of lead compounds.
- ✓ The vast majority of these compounds have never made the market place, but they have been stored in compound ‘libraries’ and are still available for testing.
- ✓ Pharmaceutical companies often screen their library of compounds whenever they study a new target.
- ✓ Pharmaceutical companies often try to diversify their range of structures by purchasing novel compounds prepared by research groups elsewhere (a useful source of revenue for hard-pressed university departments)

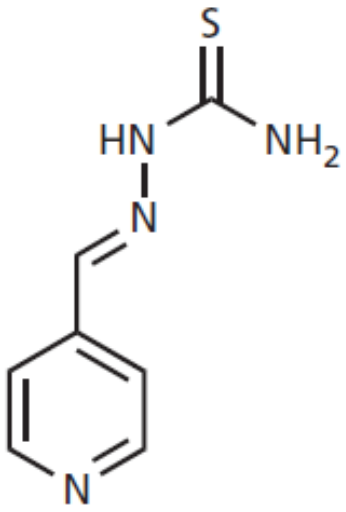
Drug discovery: finding a lead compound

3. Screening synthetic compound ‘libraries’:

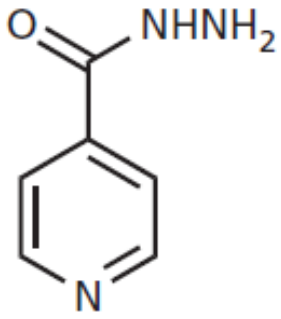
- ✓ It can also be worth testing synthetic intermediates.
- ✓ For example, a series of thiosemicarbazones was synthesized and tested as antitubercular agents in the 1950s.
- ✓ This included isonicotinaldehyde thiosemicarbazone, the synthesis of which involved the hydrazide structure isoniazid as a synthetic intermediate.
- ✓ It was found subsequently that isoniazid had greater activity than the target structure.
- ✓ Similarly, a series of quinoline- 3-carboxamide intermediates were found to have antiviral activity.

Drug discovery: finding a lead compound

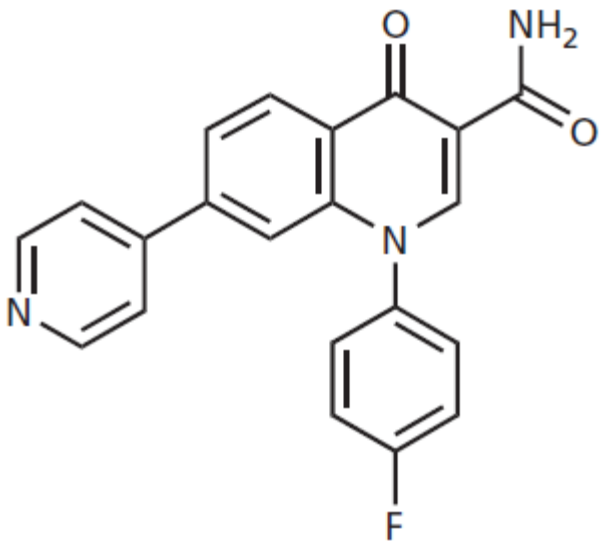
3. Screening synthetic compound ‘libraries’:



Isonicotinaldehyde thiosemicarbazone



Isoniazid



Quinoline-3-carboxamides

Drug discovery: finding a lead compound

4. Existing drugs :

➢ ‘Me too’ and ‘me better’ drugs

- ✓ Many companies use established drugs from their competitors as lead compounds in order to design a drug that gives them a foothold in the same market area.
- ✓ The aim is to modify the structure sufficiently such that it avoids patent restrictions, retains activity, and, ideally, has improved therapeutic properties.
- ✓ For example, the antihypertensive drug captopril was used as a lead compound by various companies to produce their own antihypertensive agents

Drug discovery: finding a lead compound

4. Existing drugs :

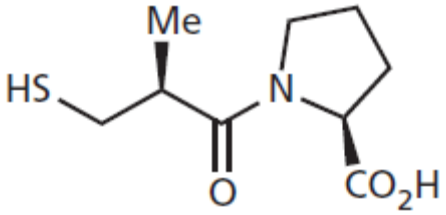
- ‘Me too’ and ‘me better’ drugs

- ✓ Although often disparaged as ‘me too’ drugs, they can often offer improvements over the original drug (‘me better’ drugs).
- ✓ For example, modern penicillins are more selective, more potent, and more stable than the original penicillins.
- ✓ Newer statins that lower cholesterol levels also have improved properties over older ones
- ✓ It should also be noted that it is not unusual for companies to be working on similar looking structures for a particular disease at the same time

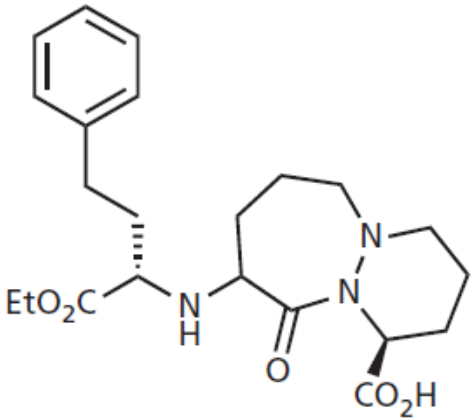
Drug discovery: finding a lead compound

4. Existing drugs :

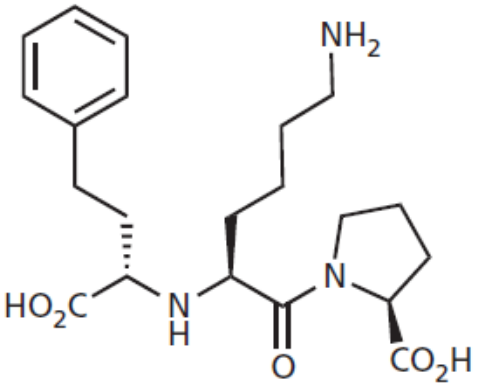
- ‘Me too’ and ‘me better’ drugs



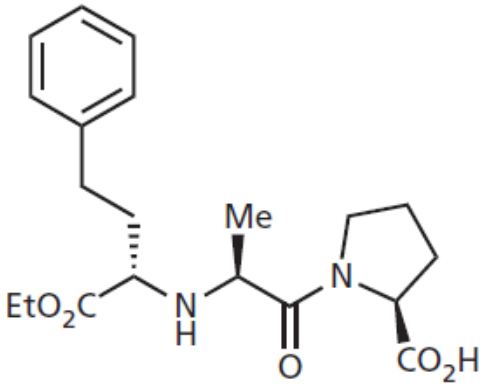
Captopril



Cilazapril
(Hoffmann-LaRoche)



Lisinopril
(Merck)



Enalapril
(Merck)

Drug discovery: finding a lead compound

4. Existing drugs :

➢ Enhancing a side effect

- ✓ An existing drug usually has a minor property or an undesirable side effect which could be of use in another area of medicine.
- ✓ As such, the drug could act as a lead compound on the basis of its side effects.
- ✓ The aim would then be to enhance the desired side effect and to eliminate the major biological activity.
- ✓ This has been described as the SOSA approach selective optimization of side activities.

Drug discovery: finding a lead compound

4. Existing drugs :

➢ Enhancing a side effect

✓ Choosing a known drug as the lead compound for a side effect has the advantage that the compound is already ‘drug-like’ and it should be more feasible to develop a clinically useful drug with the required pharmacodynamic and pharmacokinetic properties.

✓ For example, most sulphonamides have been used as antibacterial agents.

Drug discovery: finding a lead compound

4. Existing drugs :

➢ Enhancing a side effect

- ✓ some sulphonamides with antibacterial activity could not be used clinically because they had convulsive side effects brought on by hypoglycaemia (lowered glucose levels in the blood).
- ✓ Clearly, this is an undesirable side effect for an antibacterial agent, but the ability to lower blood glucose levels would be useful in the treatment of diabetes.

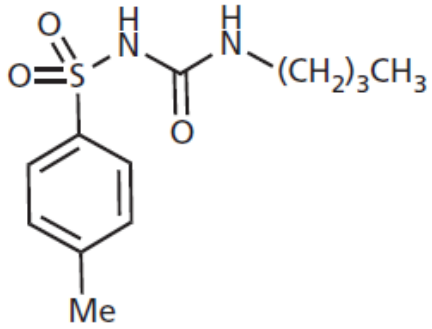
Drug discovery: finding a lead compound

4. Existing drugs :

➢ Enhancing a side effect

✓ Therefore, structural alterations were made to the sulphonamides concerned in order to eliminate the antibacterial activity and to enhance the hypoglycaemic activity.

✓ This led to the antidiabetic agent tolbutamide



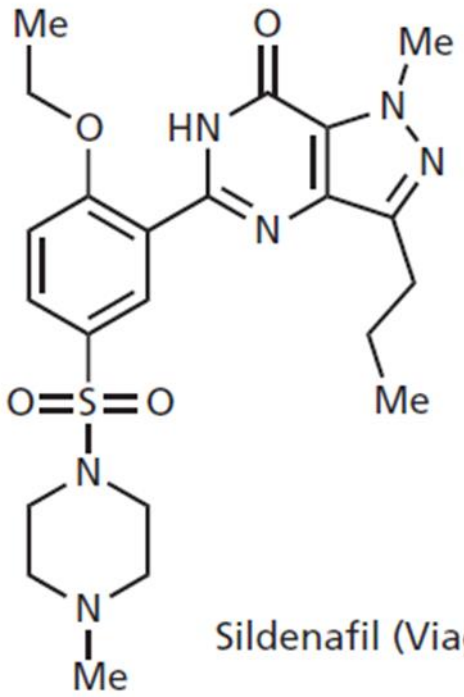
Tolbutamide

Drug discovery: finding a lead compound

4. Existing drugs :

➢ Enhancing a side effect

- ✓ In some cases, the side effect may be strong enough that the drug can be used without modification.
- ✓ For example, the anti-impotence drug sildenafil (Viagra) was originally designed as a vasodilator to treat angina and hypertension.
- ✓ During clinical trials, it was found that it acted as a vasodilator more effectively in the penis than in the heart, resulting in increased erectile function.
- ✓ The drug is now used to treat erectile dysfunction and sexual impotence.



Sildenafil (Viagra)

Drug discovery: finding a lead compound

4. Existing drugs :

- Enhancing a side effect

- ✓ Another example is the antidepressant drug bupropion.
- ✓ (act as a norepinephrine- dopamine reuptake inhibitor and nicotinic receptor antagonist)
- ✓ Patients taking this drug reported that it helped them give up smoking, and so the drug is now marketed as an antismoking aid (Zyban)

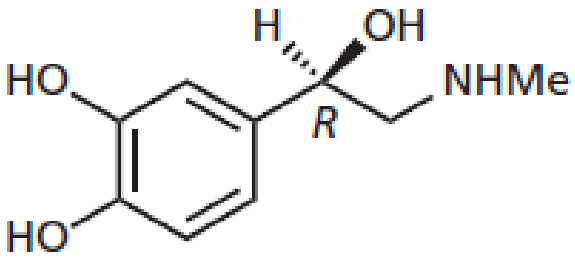
Drug discovery: finding a lead compound

5. Starting from the natural ligand or natural substrate:

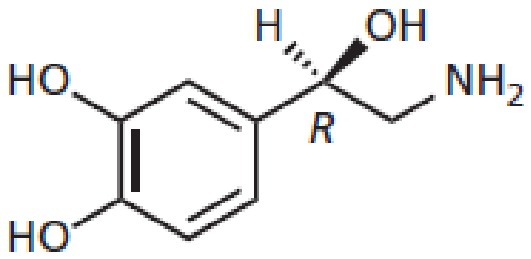
- Natural ligands for receptors

The natural ligand of a receptor can be used as the lead compound in the design of an **agonist.**

The natural ligands adrenaline and noradrenaline were the starting points for the development of adrenergic β-agonists, such as salbutamol , dobutamine , and Xamoterol



Adrenaline



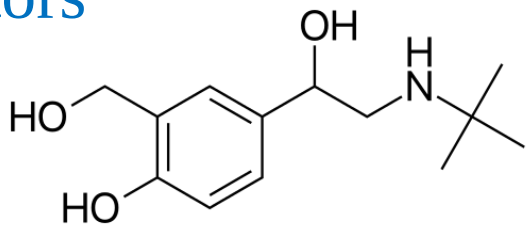
Noradrenaline

Drug discovery: finding a lead compound

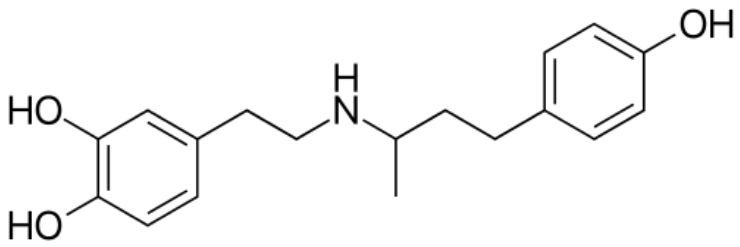
5. Starting from the natural ligand or natural substrate:

- Natural ligands for receptors

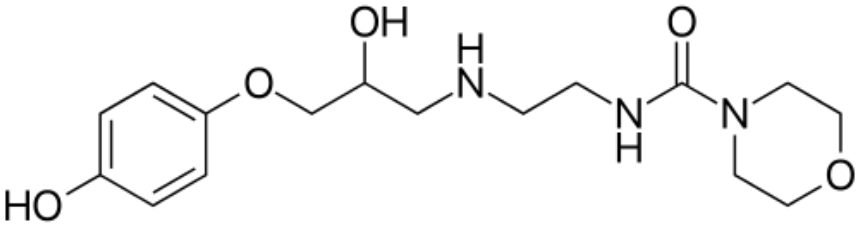
Salbutamol



Dobutamine



Xamoterol



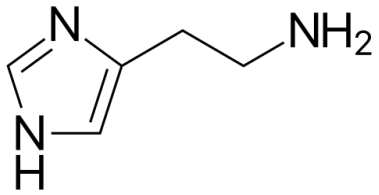
Drug discovery: finding a lead compound

5. Starting from the natural ligand or natural substrate:

- Natural ligands for receptors

The natural ligand of a receptor can be used as the lead compound in the design of an **antagonist.**

For example, histamine was used as the original lead compound in the development of the H2 histamine antagonist cimetidine



Histamine

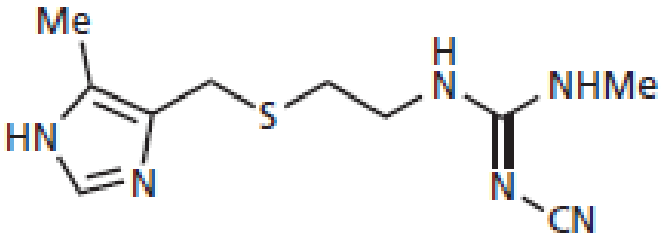


FIGURE 25.32 Cimetidine.

Drug discovery: finding a lead compound

5. Starting from the natural ligand or natural substrate:

- Enzyme products as lead compounds

✓ It should be remembered that enzymes catalyse a reaction in both directions, and so the product of an enzyme-catalysed reaction can also be used as a lead compound for an enzyme inhibitor.

✓ For example, the design of the carboxypeptidase inhibitor L-benzylsuccinic acid was based on the products arising from the carboxypeptidase -catalysed hydrolysis of peptides

Drug discovery: finding a lead compound

5. Starting from the natural ligand or natural substrate:

- Enzyme products as lead compounds

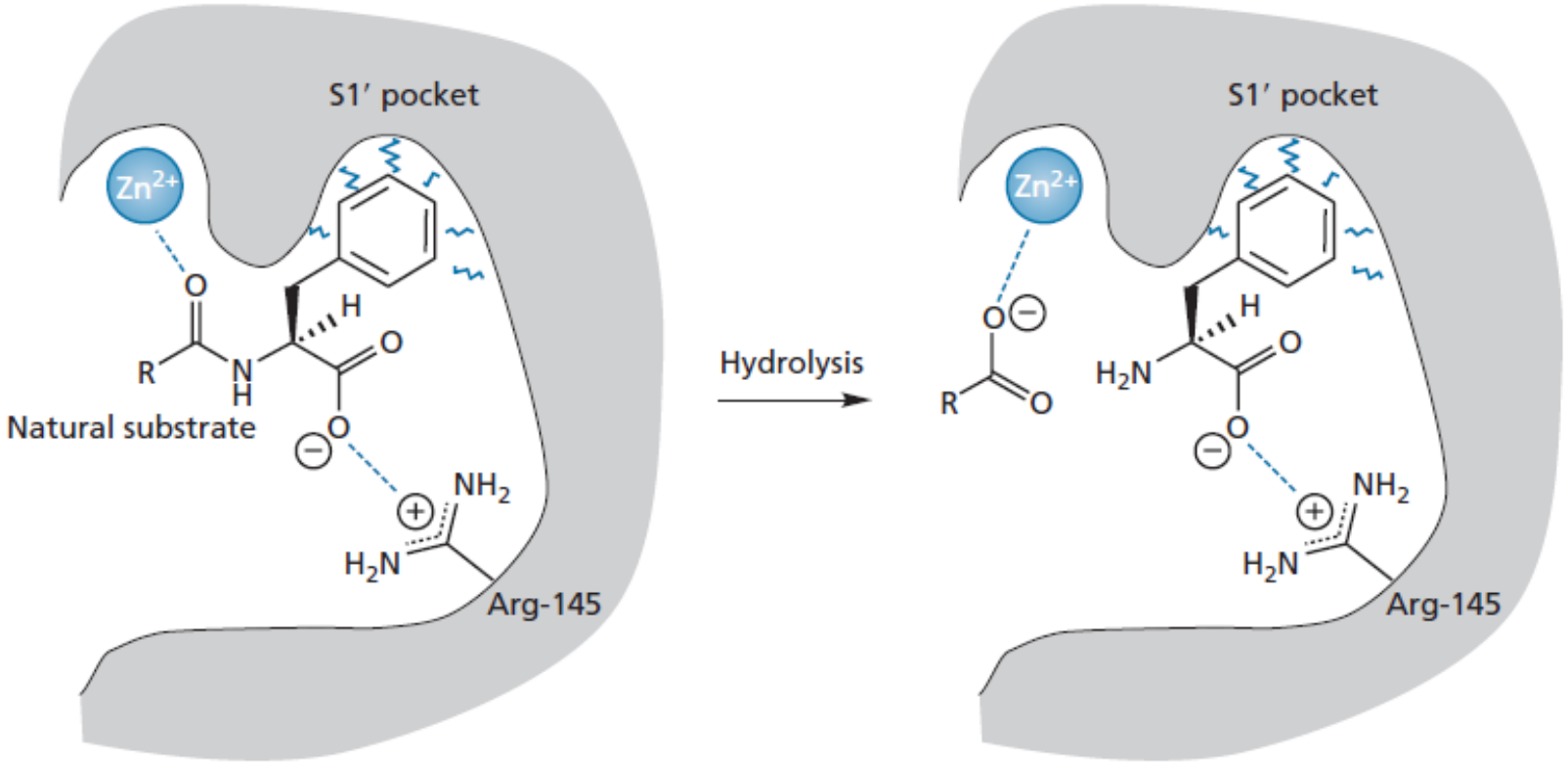


FIGURE CS2.4 Binding site interactions for a substrate bound to the active site of carboxypeptidase.

Drug discovery: finding a lead compound

5. Starting from the natural ligand or natural substrate:

- Enzyme products as lead compounds

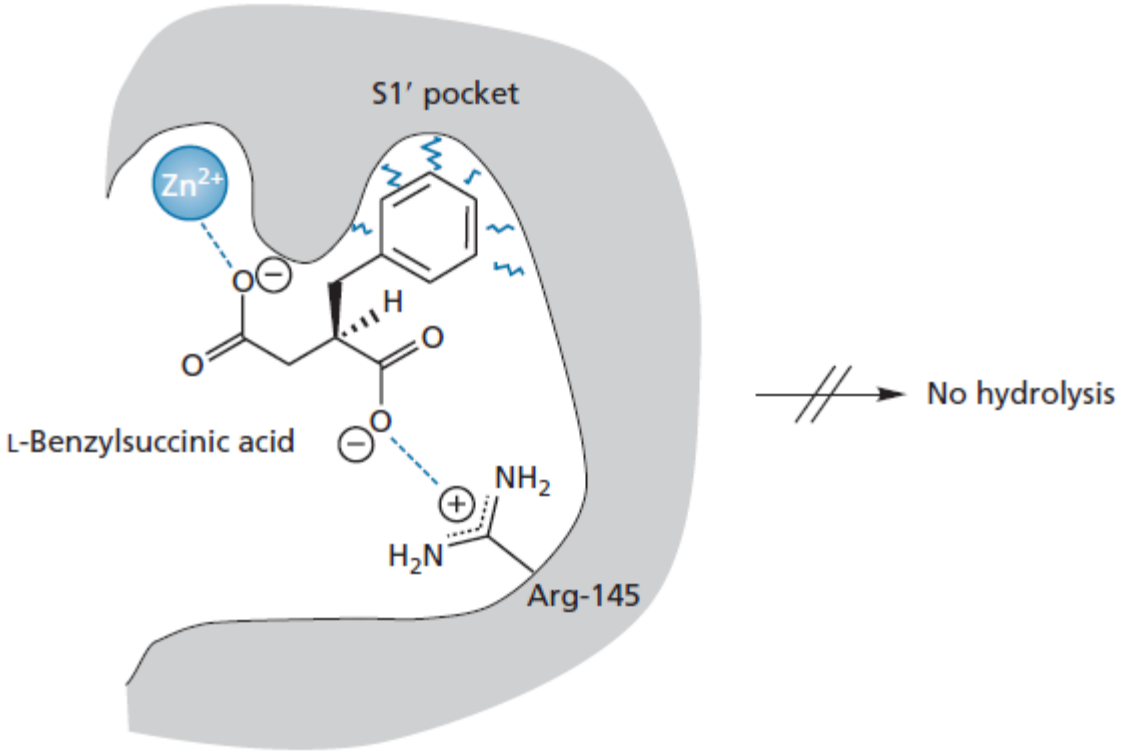


FIGURE CS2.5 Inhibition by L-benzylsuccinic acid (the *R*-enantiomer).

Drug discovery: finding a lead compound

6. Combinatorial and parallel synthesis

- ✓ The growing number of potentially new drug targets arising from genomic and proteomic projects has meant that there is an urgent need to find new lead compounds to interact with them.

- ✓ Unfortunately, the traditional sources of lead compounds have not managed to keep pace and, in the last decade or so, research groups have invested greatly in combinatorial and parallel synthesis in order to tackle this problem.

Drug discovery: finding a lead compound

6. Combinatorial and parallel synthesis

- ✓ Combinatorial synthesis is an automated solid-phase procedure aimed at producing as many different structures as possible in as short a time as possible.

- ✓ The reactions are carried out on very small scale, often in a way that will produce mixtures of compounds in each reaction vial.

- ✓ In a sense, combinatorial synthesis aims to mimic what plants do, i.e. produce a pool of chemicals, one of which may prove to be a useful lead compound.

Drug discovery: finding a lead compound

6. Combinatorial and parallel synthesis

- ✓ Parallel synthesis involves the small-scale synthesis of large numbers of compounds at the same time using specialist miniaturized equipment.

- ✓ The synthesis can be carried out in solution or solid phase, and each reaction vial contains a distinct product.

- ✓ Nowadays, parallel synthesis is generally preferred over combinatorial synthesis in order to produce smaller, more focused compound libraries.

Drug discovery: finding a lead compound

7. Computer-aided design of lead compounds

- ✓ A detailed knowledge of a target binding site aids significantly in the design of novel lead compounds intended to bind with that target.
- ✓ In cases where enzymes or receptors can be crystallized, it is possible to determine the structure of the protein and its binding site by X-ray crystallography.
- ✓ Molecular modelling soft ware programs can then be used to study the binding site and to design molecules which will fit and bind to the site - de novo drug design.
- ✓ In some cases, the enzyme or receptor cannot be crystallized and so X-ray crystallography cannot be carried out.
- ✓ if the structure of an analogous protein has been determined, this can be used as the basis for generating a computer model of the protein.

Drug discovery: finding a lead compound

8. Serendipity and the prepared mind

- ✓ Frequently, lead compounds are found as a result of serendipity (i.e. chance).
- ✓ serendipity still needs someone with a prepared mind to recognize the significance of chance discoveries and to take advantage of these events.

- ✓ The discovery of cisplatin and penicillin are two such examples, but there are many more

Drug discovery: finding a lead compound

8. Serendipity and the prepared mind

- ✓ Sometimes, the research carried out to improve a drug can have unexpected and beneficial results.

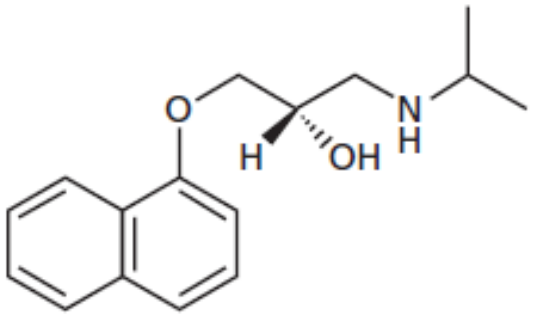
- ✓ For example, propranolol and its analogues are effective β-blockers (antagonists of β-adrenergic receptors)
- ✓ they are also lipophilic, which means that they can cross the blood–brain barrier and cause central nervous system (CNS) side effects.

- ✓ To counteract this, more hydrophilic analogues were designed by decreasing the size of the aromatic ring system and adding a hydrophilic amide group.

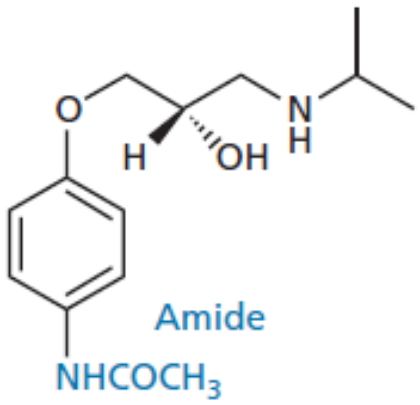
Drug discovery: finding a lead compound

8. Serendipity and the prepared mind

- ✓ Sometimes, the research carried out to improve a drug can have unexpected and beneficial results.
- ✓ One of the compounds made was practolol . As expected, this compound had fewer CNS side effects, but, more importantly, it was found to be a selective antagonist for the β1-receptors of the heart over β-receptors in other organs—a result that was highly desirable, but not the one that was being looked for at the time.



Propranolol



Practolol

Drug discovery: finding a lead compound

9. Computerized searching of structural databases

- ✓ New lead compounds can be found by carrying out computerized searches of structural databases.
- ✓ In order to carry out such a search, it is necessary to know the desired pharmacophore.
- ✓ Alternatively, docking experiments can be carried out if the structure of the target binding site is known

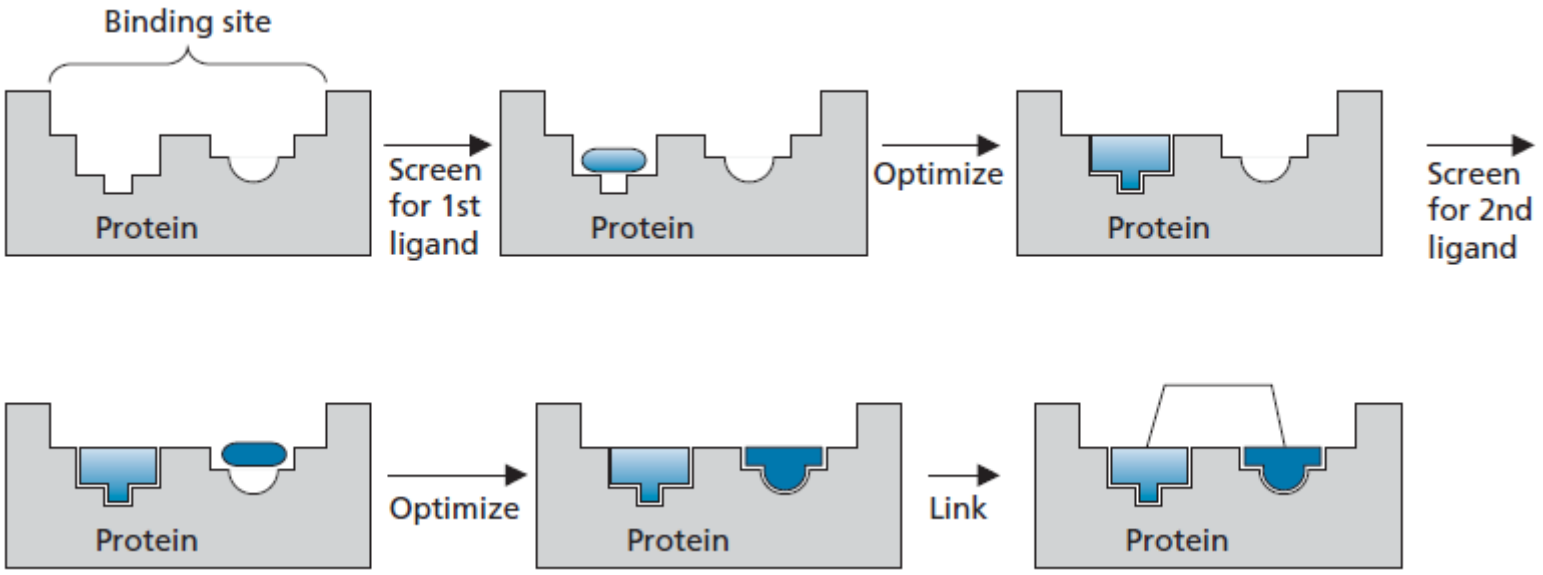
Drug discovery: finding a lead compound

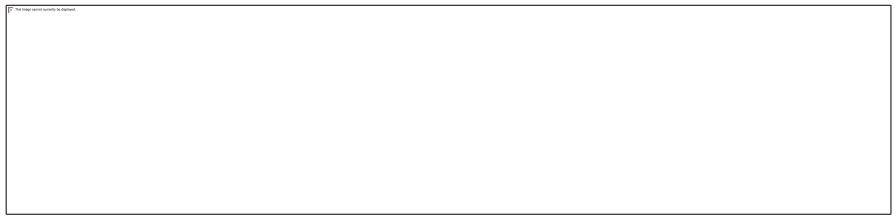
10. Fragment-based lead discovery

- ✓ Recently, NMR spectroscopy has been used to design a lead compound rather than to discover one.
- ✓ In essence, the method sets out to find small molecules (epitopes), which will bind to specific, but different, regions of a protein's binding site.
- ✓ These molecules will have no activity in themselves as they only bind to one part of the binding site, but if a larger molecule is designed which links these epitopes together, then a lead compound may be created which is active and which binds to the whole of the binding site

Drug discovery: finding a lead compound

10. Fragment-based lead discovery





Thank You!