Medicinal Chemistry

Drug discovery, design, and development

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Drug discovery, design, and development

The Past

- **Before the twentieth century, medicines consisted mainly of herbs and potions جَروعات.**

- **It was not until the mid-nineteenth century that the first serious efforts were made to isolate and purify the active principles of these remedies**

- **The success of these efforts led to the birth of many of the pharmaceutical companies we know today.**

- **Since then, many naturally occurring drugs have been obtained and their structures determined (e.g. morphine from opium, cocaine from coca leaves, quinine from the bark of the cinchona tree).**

Drug discovery, design, and development

The Past

- **These natural products sparked off a major synthetic effort where chemists made literally thousands of analogues in an attempt to improve on what nature had provided.**

- **Research very much focused on what is known as the lead compound ,an active principle isolated from a natural source or a synthetic compound prepared in the laboratory.**

Drug discovery, design, and development

The present

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

I. Drug discovery (finding a lead)

- 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 if necessary.

Drug discovery, design, and development

The present

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

II. Drug design

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

Drug discovery, design, and development

The present

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

III. 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, design, and development

The present

- Many of these stages run concurrently and are dependent on each other.
- For example, preclinical trials are usually carried out in parallel with the development of a manufacturing process.
- Even so, the discovery, design and development of a new drug can take 15 years or more, involve the synthesis of over 10 000 compounds and cost in the region of $800 million or E450 million.

I. Drug discovery (finding a lead)

1. Choosing a disease

- How does a pharmaceutical company decide which disease to target when designing a new drug?

1) Concentrate on diseases where there is a need for new drugs.

2) Pharmaceutical companies, however, have to consider economic factors as well as medical ones.

As a result,

- research projects tend to focus on diseases that are important in the developed world, because this is the market best able to afford new drugs.

I. Drug discovery (finding a lead)

1. Choosing a disease

- **A great deal of research is carried out on ailments such as:**
  migraine,
  depression,
  ulcers,
  obesity,
  flu,
  cancer, and
  cardiovascular disease.

- **Less is carried out on the tropical diseases of the developing world. Only when such diseases start to make an impact in richer countries do the pharmaceutical companies sit up and take notice (antimalarial research).**

I. Drug discovery (finding a lead)

2 . Choosing a drug target

2.1- Drug targets

- **Once a therapeutic area has been identified, the next stage is:**

1) **To identify a suitable drug target (e.g. receptor, enzyme, or nucleic acid).**
2) **To identify whether agonists or antagonists should be designed for a particular receptor, or whether inhibitors should be designed for a particular enzyme.**

I. Drug discovery (finding a lead)

2 . Choosing a drug target

2.1- Drug targets

❑ **Drug targets are most often proteins, but nucleic acids may also be attractive targets for some diseases.**

TARGET	MECHANISM
• Enzyme Inhibitor	- Reversible or irreversible
• Receptor*	- Agonist or antagonist
• Nucleic acid	- Intercalator (binder), modifier (alkylating agent) or substrate mimic.
• Ion channels*	- Blockers or openers(diazoxide and minoxidil)
• Transporters*	- Uptake inhibitors(SSRI)

*present in the cell membranes

I. Drug discovery (finding a lead)

2 . Choosing a drug target

2.1- Drug targets

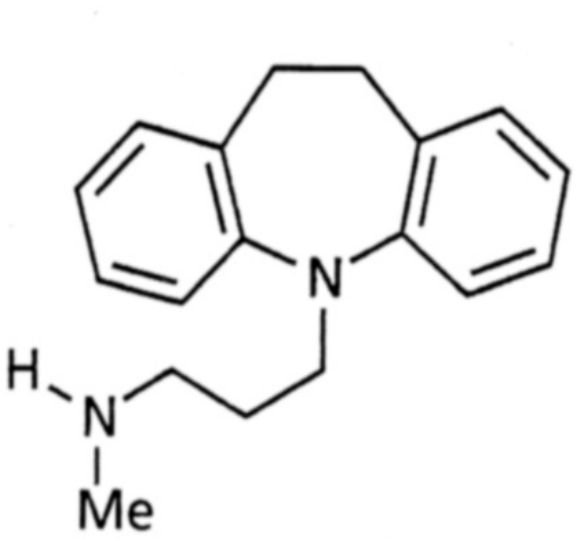
- Sometimes it is not known for certain whether a particular target will be suitable or not.

For example, tricyclic antidepressants such as desipramine (Fig. 9.1) are known to inhibit the uptake of the neurotransmitter noradrenaline from nerve synapses by inhibiting the carrier protein for noradrenaline. However, these drugs also inhibit uptake of a separate neurotransmitter, called serotonin, and the possibility arose that inhibiting serotonin uptake might also be beneficial.

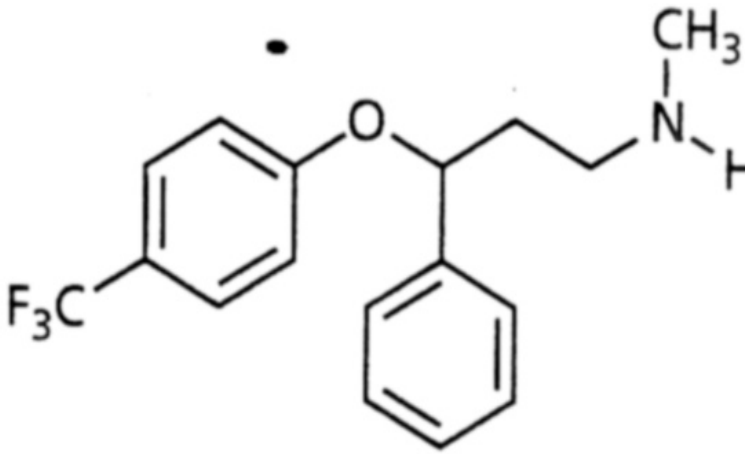
A search for selective serotonin reuptake inhibitors (SSRIs) was initiated, which led to the discovery of the best-selling antidepressant drug fluoxetine (Prozac) (Fig. 9.1),

2 Choosing a drug target

2.1- Drug targets



Desipramine



Fluoxetine (Prozac) **(SSRIs)**

Figure 9.1 Antidepressant drugs.

I. Drug discovery (finding a lead)

2 Choosing a drug target

2 . 2 Discovering drug targets

If a drug or a poison produces a biological effect, there must be a molecular target for that agent in the body.

- **In the past, the discovery of drug targets depended on finding the drug first (the analgesic morphine interact with a molecular target in the human body).**

  As this involves coincidence more than design, the detection of drug targets was very much *a hit and miss affair.*

- **Later, the body's own chemical messengers started to be discovered and pointed the finger at further targets.**

I. Drug discovery (finding a lead)

2 Choosing a drug target

2.3 Target specificity and selectivity between species

The more selective a drug is for its target, the less chance that it will interact with different targets and have undesirable side effects.

1) **In the field of antimicrobial agents, the best targets to choose are those that are: 1) unique to the microbe and 2) are not present in humans. For example:**

-penicillin targets an enzyme involved in bacterial cell wall biosynthesis. Mammalian cells do not have a cell wall, so this enzyme is absent in human cells and penicillin has few side effects.

- sulfonamides inhibit a bacterial enzyme not present in human cells .

- several agents used to treat AIDS (acquired immune deficiency syndrome مُتَلازِمَةُ العَوَزِ المَناعِيِّ المُكْتَسَب) inhibit an enzyme called retroviral reverse transcriptase مُنْتَسِخَة فَيْرُوْسٌ قَهْقَرِيّ which is unique to the infectious agent HIV (human immunodeficiency virus فَيروسُ العَوَزِ المَناعِيِّ البَشَرِيّ).

I. Drug discovery (finding a lead)

2 Choosing a drug target

2 .3 Target specificity and selectivity between species

2) It is still possible to design drugs against targets which are present both in humans and in microbes, as long as the drugs show selectivity against the microbial target:

An enzyme which catalyses a reaction in a bacterial cell differs significantly from the equivalent enzyme in a human cell

The antifungal agent fluconazole (Fig. 9.2) inhibits a fungal demethylase enzyme involved in steroid biosynthesis. This enzyme is also present in humans, but the structural differences between the two enzymes are significant enough that the antifungal agent is highly selective for the fungal enzyme.

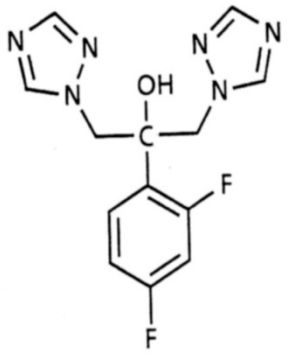


Figure 9.2 Fluconazole.

I. Drug discovery (finding a lead)

2 Choosing a drug target

2 .4 Target specificity and selectivity within the body

Selectivity is also important for drugs acting on targets within the body.

1. **Enzyme inhibitors should only inhibit the target enzyme and not some other enzyme(selectivity between the various isoezymes of an enzyme).**

2. **Receptor agonists/antagonists should ideally interact with a specific kind of receptor (e.g. the adrenergic receptor) rather than a variety of different receptors.**

   Receptor agonists and antagonists should not only show selectivity for a particular receptor (e.g. an adrenergic receptor) or even a particular receptor type (e.g. the β -adrenergic receptor), but also for a particular receptor subtype (e.g. the β_2-adrenergic receptor).

I. Drug discovery (finding a lead)

2 Choosing a drug target

2 .5 Targeting drugs to specific organs and tissues

1) **Targeting drugs against specific receptor subtypes often allows drugs to be targeted against specific organs or against specific areas of the brain:**

This is because the various receptor subtypes are not uniformly distributed around the body, but are often concentrated in particular tissues.

For example, the (β-adrenergic receptors in the heart are predominantly β_1 whereas those in the lungs are β_2. This makes it feasible to design drugs that will work on the lungs with a minimal side effect on the heart, and vice versa.

I. Drug discovery-finding a lead

2 Choosing a drug target

2.5 Targeting drugs to specific organs and tissues

2) Many research projects set out to discover new drugs with a defined profile of activity against a range of specific targets.

For example, a research team may set out to find a drug that has agonist activity for one receptor subtype and antagonist activity at another.

I. Drug discovery-finding a lead

2 Choosing a drug target

2 .6 Pitfalls

I. **the body is a highly complex system. For any given function, there are usually several messengers, receptors, and enzymes involved in the process.**

For example, **there is no one simple cause for hypertension (high blood pressure).** This is illustrated by the **variety of receptors** and **enzymes** which can **be targeted in its treatment**. These include:

- **β1-adrenoceptors (β blockers),**
- **calcium ion channels (Calcium Antagonists)**
- **angiotensin-converting enzyme (ACEI), and**
- **potassium ion channels (potassium ion channels openers)**

I. Drug discovery-finding a lead

2 Choosing a drug target

2 .6 Pitfalls

II. As a result, more than one target may need to be addressed for a particular ailment. For example,

most of the current therapies for asthma involve a combination of a bronchodilator (β_2 -agonist) and an antiinflammatory agent such as a corticosteroid.

III. Sometimes, drugs designed against a specific target become less effective over time. Because cells have a highly complex system of signalling mechanisms, it is possible that the blockade of one part of that system could be bypassed(Figure 9.3).

I. Drug discovery-finding a lead

2 Choosing a drug target

2 .6 Pitfalls

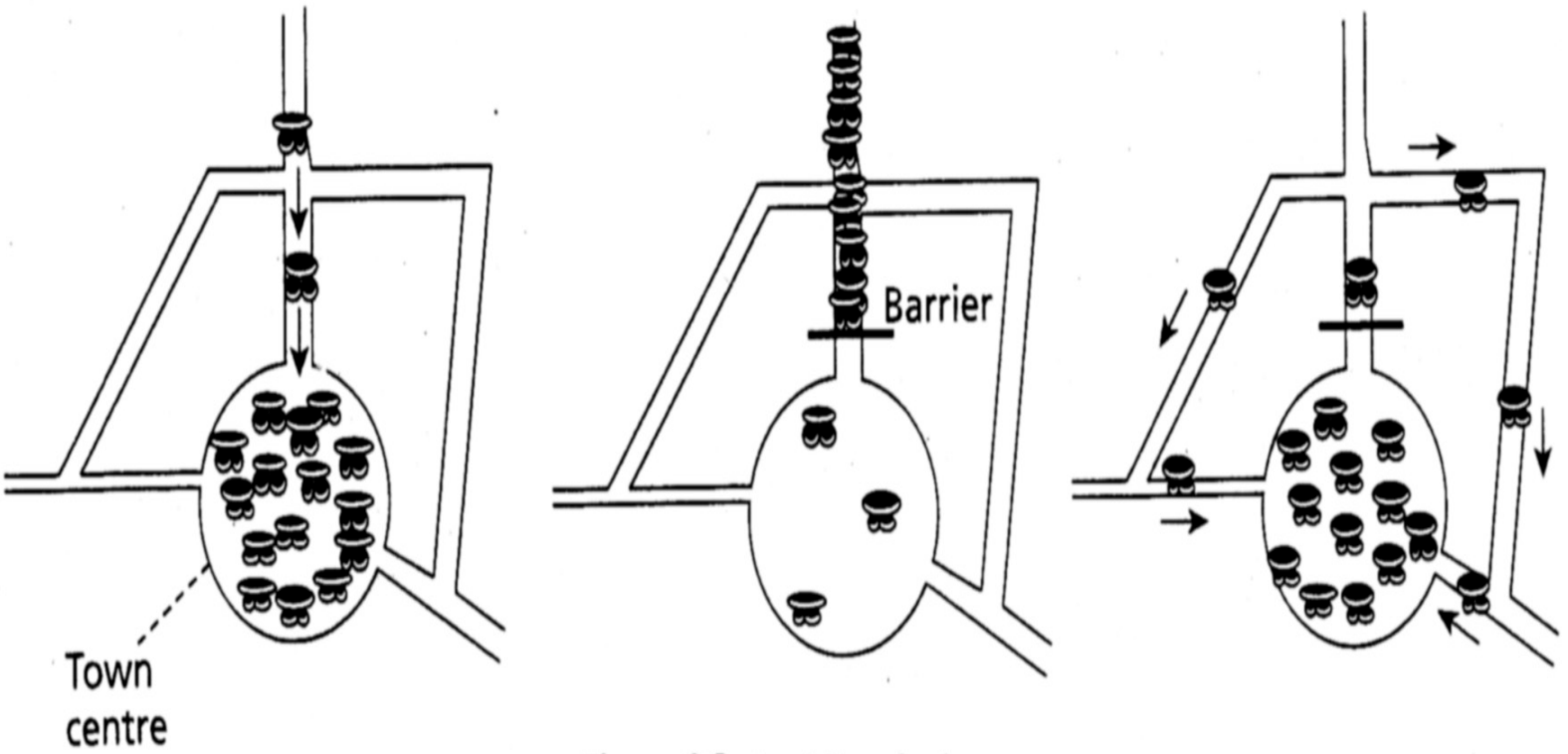


Figure 9.3 Avoiding the jam.

3 Identifying a bioassay

3.1 Choice of bioassay

1- Choosing the right bioassay or test system is crucial to the success of a drug research programme.

- **The test should be** :

  1) simple, 2) quick, and 3) relevant, as there is usually a large number of compounds to be analyzed.

- **Human testing is not possible at such an early stage, so the test has to be done :**

in vitro (i.e. **on isolated cells, tissues, enzymes, or receptors**) or

in vivo (**on animals**).

3 Identifying a bioassay

3.1 Choice of bioassay

2 - In general,

in vitro tests are preferred over *in vivo* tests because they are:

1- cheaper,

2- easier to carry out,

3- less controversial, and they

4- can be automated. However,

in vivo tests are often needed :

- to check whether drugs interacting with a specific target have the desired pharmacological activity, and also

- to monitor their pharmacokinetic properties.

3 Identifying a bioassay

3. 2 Test validity

1) **Sometimes the validity of testing procedures** is **easy** and **clear-cut:**

- **An antibacterial agent can be tested in vitro by measuring how effectively it kills bacterial cells.**

- **A local anaesthetic can be tested in vitro on how well it blocks action potentials in isolated nerve tissue.**

3 Identifying a bioassay

3.2 Test validity

2) In other cases, the testing procedure is more difficult:

how do you test a new antipsychotic drug? There is no animal model for this condition and so a simple *in vivo* test is not possible. One way round this problem is:

- **to propose which receptor or receptors might be involved in a medical condition and**
- **to carry out *in vitro* tests against these in the expectation that the drug will have the desired activity when it comes to clinical trials.**

3 Identifying a bioassay

3.3 High-throughput screening (HTS).

Robotics and the miniaturization of *in vitro* tests on genetically modified cells has led to a process called high-throughput screening (HTS).

This involves the automated testing of large numbers of compounds versus a large number of targets; typically,

several thousand compounds can be tested at once in 30 -50 biochemical tests. It is important that the test should produce an easily measurable effect which can be detected and measured automatically. This effect could be

1) **cell growth**,
2) **an enzyme-catalyzed reaction which produces a colour change**, or
3) **displacement of radioactively labelled ligands** from receptors.

4 Finding a lead compound

- Once a **target** and a **testing system** have been chosen, the **next stage is to find a lead compound** - ***a compound which shows the desired pharmaceutical and pharmacological activities.***

- The **level of activity may not be very great and there may be undesirable side effects , but the lead compound provides a start for the drug design and development process.**

- There are **various ways(8) in which a lead compound might be discovered as described in the following sections.**

I. Drug discovery-finding a lead

4 Finding a lead compound

4.1 Screening of natural products

1) Natural products are a rich source of biologically active compounds.

2) 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.

3) Usually, the natural source has the active principle: Such a structure can act as a lead compound.

4) Most biologically active natural products are secondary metabolites with quite complex structures : extremely novel compounds. Unfortunately, this complexity also makes their synthesis difficult and the compound usually has to be extracted from its natural source:

   a slow, expensive, and inefficient process.

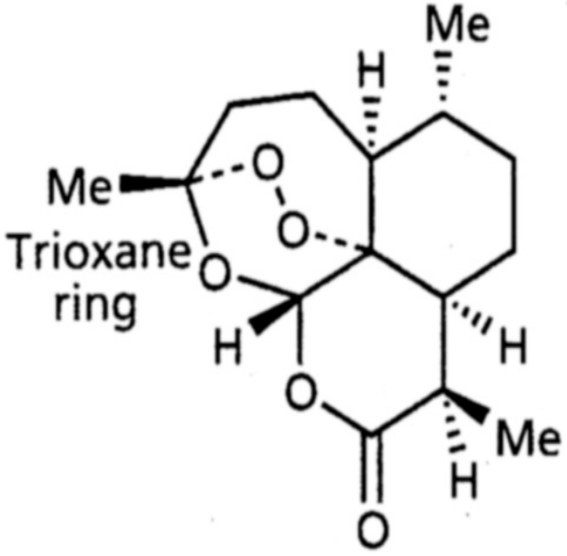
I. Drug discovery-finding a lead

4 Finding a lead compound

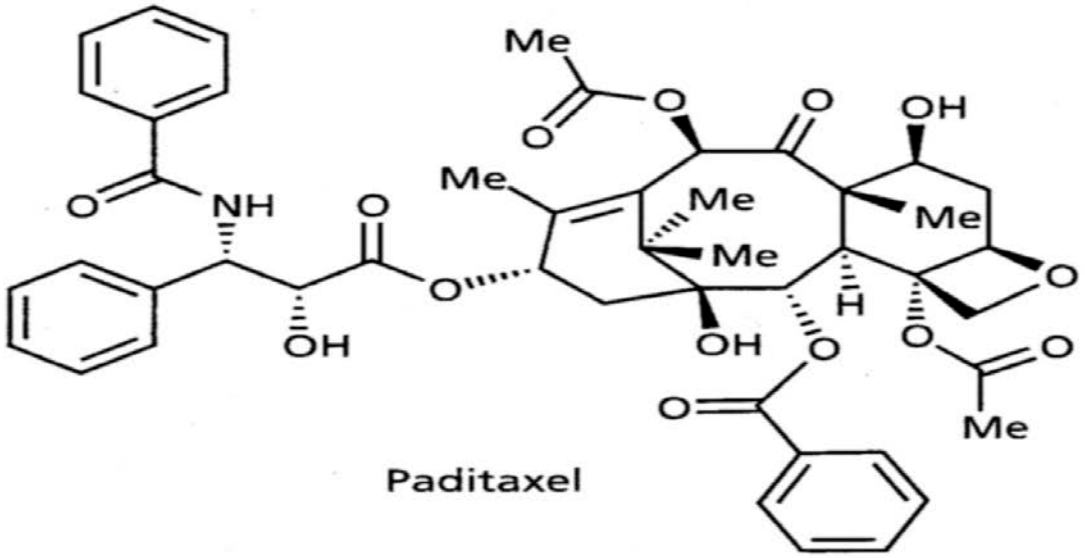
4.1 Screening of natural products

5) Many natural products have radically new chemical structures which no chemist would dream of synthesizing:

the antimalarial drug artemisinin (Fig. 9.5) is a natural product with an extremely unstable looking trioxane ring - one of the most unlikely structures to have appeared in recent years.



Artemisinin



Paditaxel

Figure 9.5 Plant natural products as drugs.

I. Drug discovery-finding a lead

4 Finding a lead compound

4.1 Screening of natural products

4.1.1 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).

Clinically useful drugs which have recently been isolated from plants include the anticancer agent paclitaxel (Taxol) from the yew tree, and the antimalarial agent artemisinin from a Chinese plant (Fig. 9.5).

I. Drug discovery-finding a lead

4 Finding a lead compound

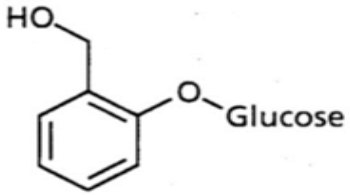
4.1 Screening of natural products

4.1.1 The plant kingdom

Willow bark لحاء الصفصاف and salicylic acid

Doctrine of Signatures

The Rev Edward Stone (1760s) searched along a riverbank (i.e. a cold and wet place) for a plant-based cure for the fevers associated with influenza. Found that the bark of the willow was effective in reducing fever.



Salicin

Native American Cherokees used willow bark for such purposes for centuries.

willow bark contains salicin →

* **metabolized *in vivo* to the active agent salicylic acid →**
* **salicylic acid and more tolerable "prodrug" aspirin made in late 19th century1899 → mechanism of action not discovered until the 1970s.**

I. Drug discovery-finding a lead

4 Finding a lead compound

4.1 Screening of natural products

4.1.2 The microbial world

Microorganisms such as bacteria and fungi have also provided rich pickings for drugs and lead compounds.

1) **The screening of microorganisms became highly popular after the discovery of penicillin, cephalosporins, tetracyclines, aminoglycosides, rifamycins, and chloramphenicol.**

2) **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, asperlicin - isolated from *Aspergillus alliaceus*--is a novel antagonist of a peptide hormone called cholecystokinin (CCK) which is involved in the control of appetite.**

4 Finding a lead compound

4.1 Screening of natural products

4.1.2 The microbial world

3) Other examples include the **fungal metabolite lovastatin**, which was the **lead compound** for a series of drugs that **lower cholesterol levels,** and **another fungal metabolite** called **ciclosporin** (Fig. 9.6) which is used to **suppress the immune response** after transplantation operations .

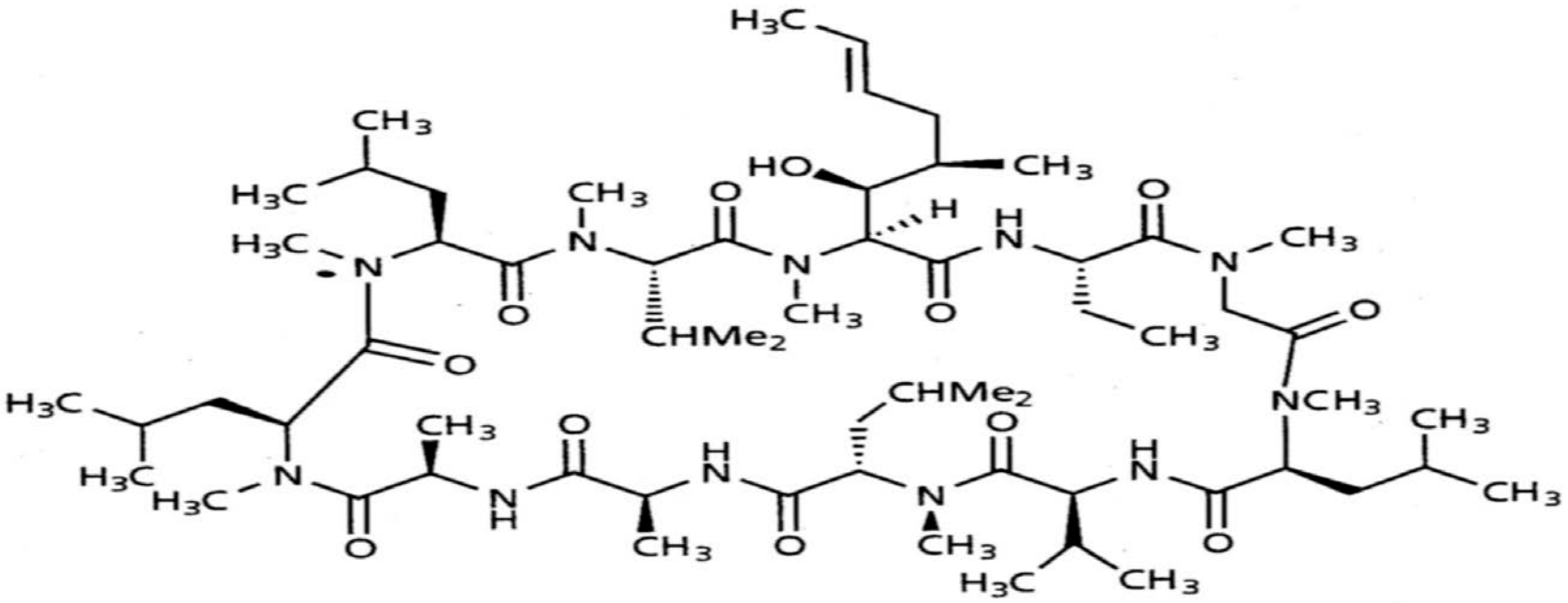


Figure 9.6 Ciclosporin.

I. Drug discovery-finding a lead

4 Finding a lead compound

4.1 Screening of natural products

4.1.3 Venoms and toxins

Venoms سُم and toxins ذيفان from animals, plants, snakes, spiders, scorpions, insects, and microorganisms are extremely potent because they often have very specific interactions تآثر 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 the lead compound for the development of the antihypertensive agents cilazapril and captopril.

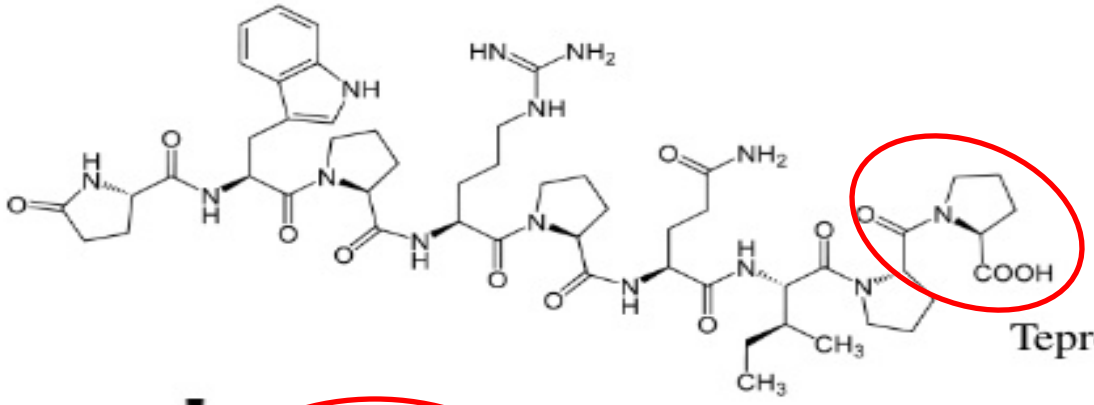
I. Drug discovery-finding a lead

4 Finding a lead compound

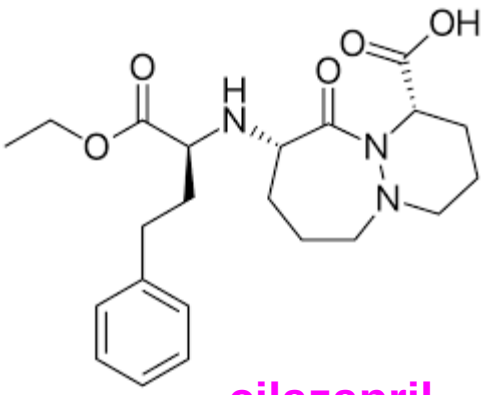
4.1 Screening of natural products

4.1.3 Venoms and toxins

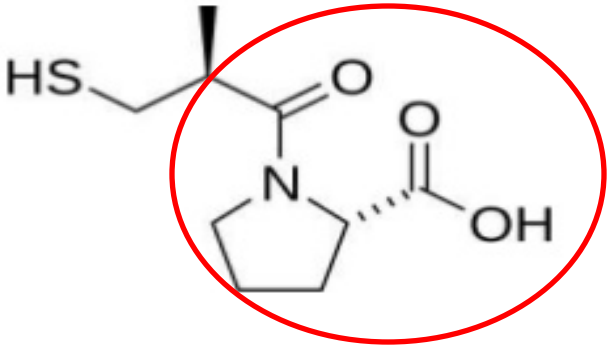
Eg: Teprotide a peptide isolated from the venom of Brazilian viper, was a lead compound for the development of the antihypertension agent **captopril.**



Teprotide



cilazapril



Captopril

I. Drug discovery-finding a lead

4 Finding a lead compound

4.1 Screening of natural products

4.1.3 Venoms and toxins

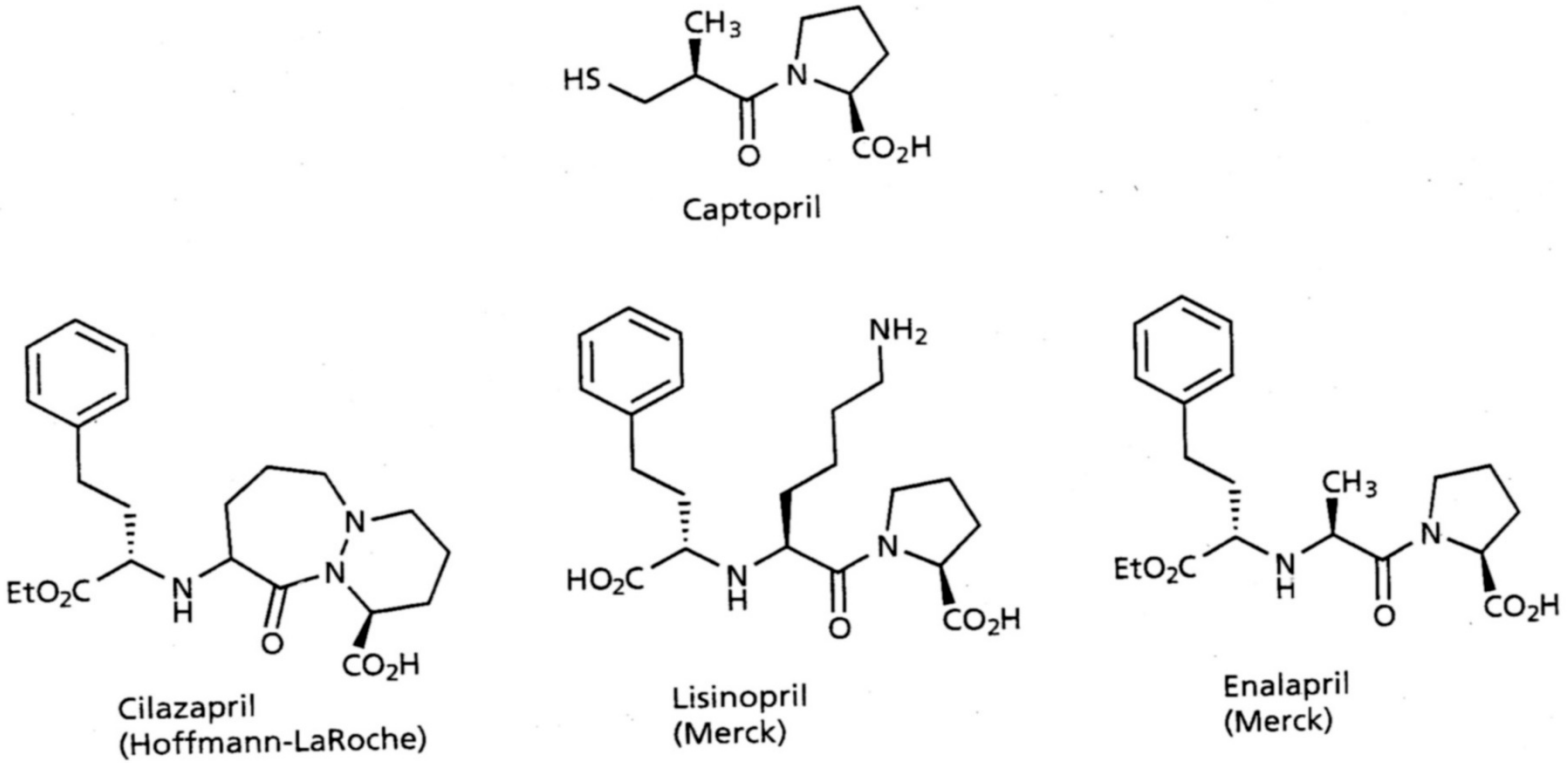


Figure 9.10 Captopril and 'me too' drugs.

4 Finding a lead compound

4.2 Medical folklore

In the past, ancient civilizations depended greatly on local flora نَبيت and fauna حَيَوَانَاتُ المِنْطَقَة for their survival. They would experiment with various berries, leaves, and roots to find out what effects they had.

1) **Rhubarb root has been used as a purgative for many centuries,. In China, it was called `The General' because of its `galloping charge'! The most significant chemicals in rhubarb root are anthraquinones, which were used as the lead compounds in the design of the laxative dantron (Fig. 9.8).**

4 Finding a lead compound

4.2 Medical folklore

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

3) The therapeutic properties of the opium poppy (active principle morphine) were known in Ancient Egypt,

4) As were those of the *Solanaceae* البانِجانِيَّلت plants in ancient Greece (active principles atropine and hyoscine;.

5) The snakeroot plant (Rauwolfia serpentinawas) well regarded in India (active principle reserpine;,

4 Finding a lead compound

4.2 Medical folklore

6) Herbalists in medieval England used extracts from the willow tree (salicin; Fig. *9.8)* and foxglove (active principle digitalis - a mixture of compounds such as digitoxin, digitonin, and digitalin).

7) The Aztec and Mayan cultures of South America used extracts from a variety of bushes and trees including the ipecacuanha root عِرْقُ الذَّهَب (active principle emetine; Fig. 9.8), coca bush (active principle cocaine), and cinchona bark (active principle quinine).

I. Drug discovery-finding a lead

4 Finding a lead compound

4.2 Medical folklore

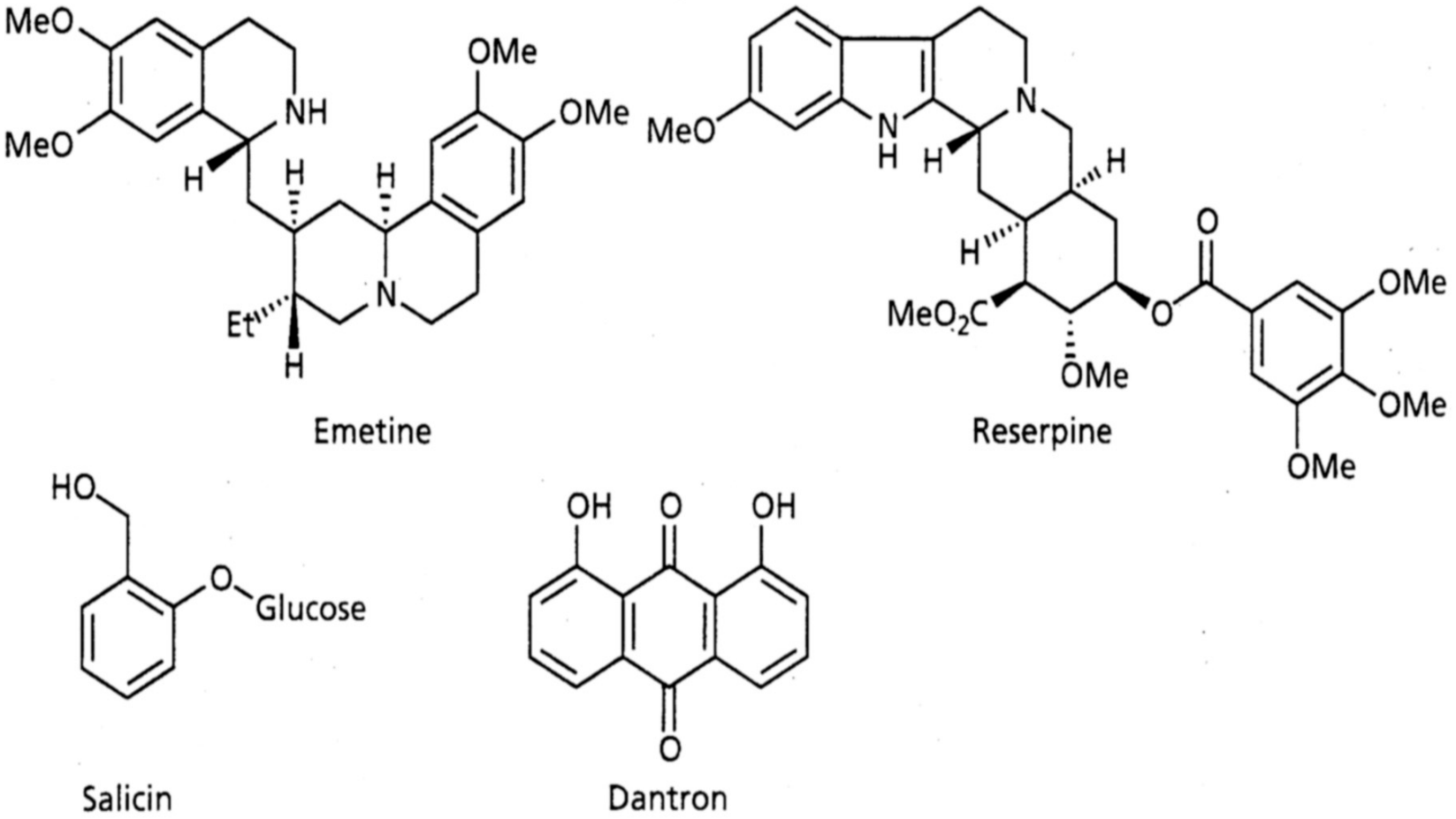


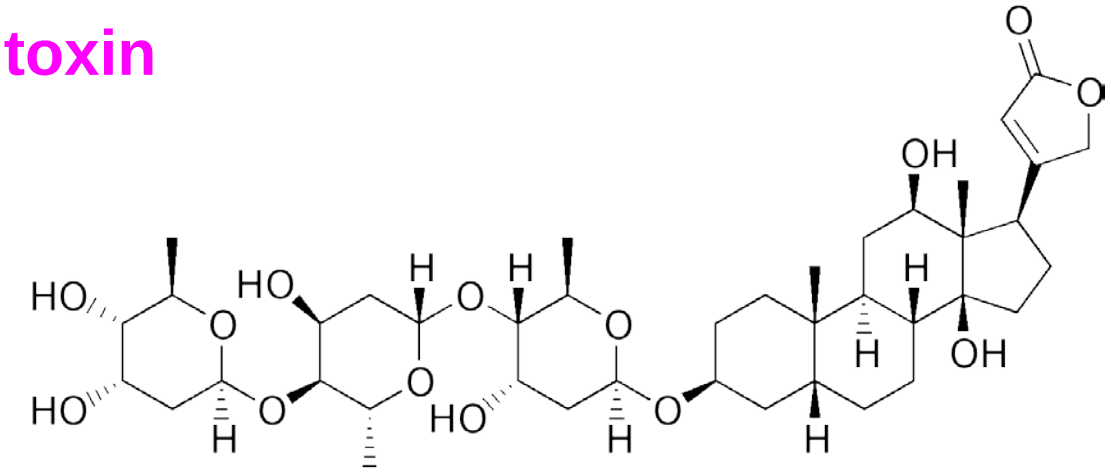
Figure 9.8 Active compounds resulting from studies of herbs and potions.

I. Drug discovery-finding a lead

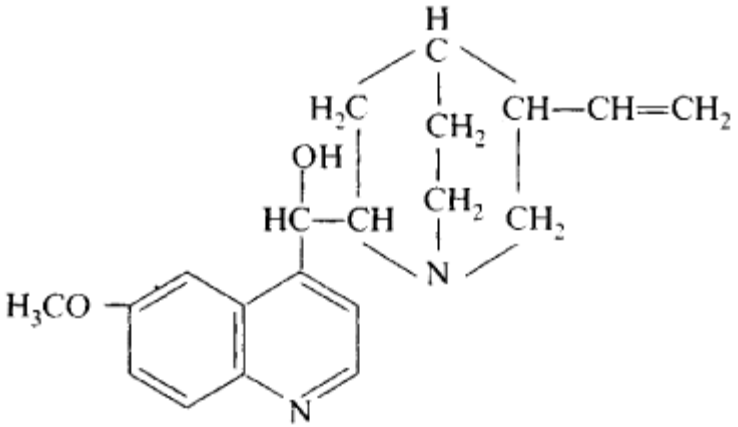
4 Finding a lead compound

4.2 Medical folklore

digitoxin

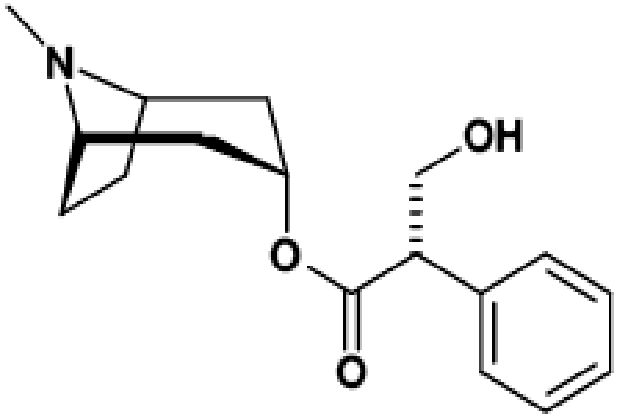


quinine

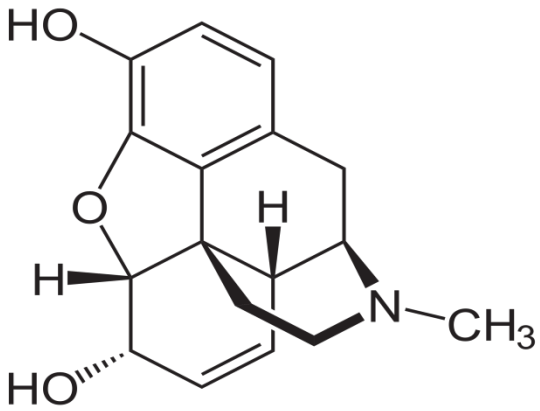


4 Finding a lead compound

4.2 Medical folklore



Atropine



morphine

4 Finding a lead compound

4. 3 Screening synthetic compound 'libraries'

1. The thousands of compounds which have been synthesized by the pharmaceutical companies over the years are another source of lead compounds.

2. 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.

3. Pharmaceutical companies often screen their library of compounds whenever they study a new target.

4 Finding a lead compound

4.3 Screening synthetic compound 'libraries'

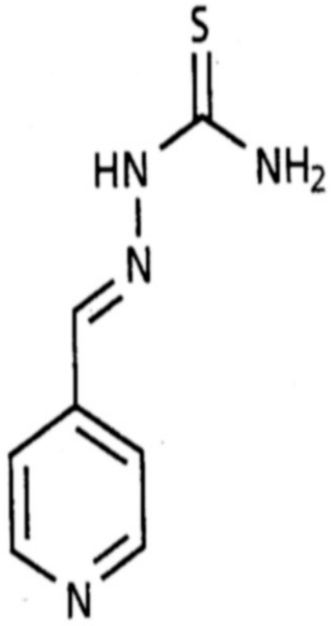
4. **It can also be worth testing synthetic intermediates**. For example, a series of **thiosemicarbazones** were synthesized and tested as **antitubercular agents** in the **1950s**. They included **isonicotinaldehyde thiosemicarbazone, the synthesis of which involved the hydrazide structure isoniazid** (fig. 9,9) **as a synthetic intermediate.**

5. **It was subsequently found that isoniazid had greater activity than the target structure**.

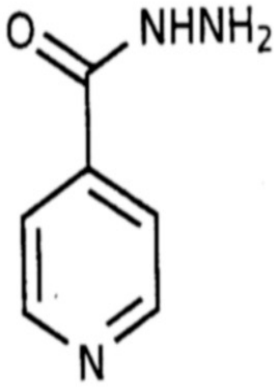
6. **Similarly, a series of quinoline-3-carboxamide intermediates (Fig. 9.9) were found to have antiviral activity.**

4 Finding a lead compound

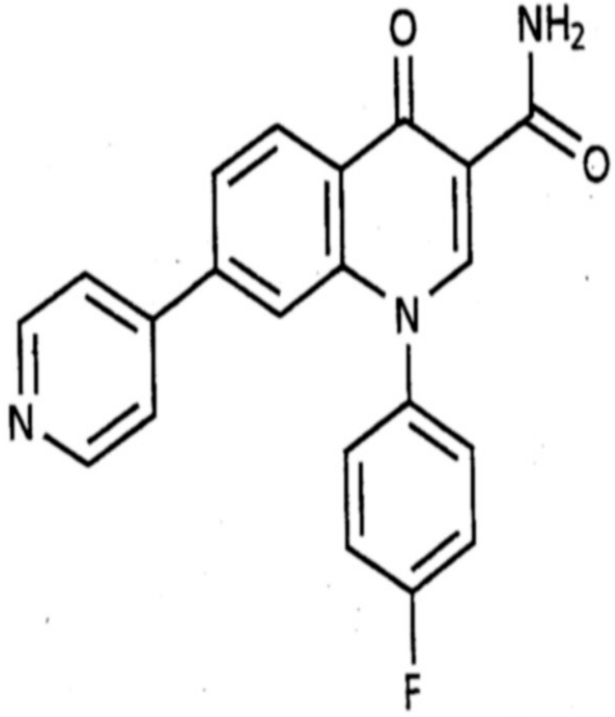
4.3 Screening synthetic compound 'libraries'



Isonicotinaldehyde thiosemicarbazone



Isoniazid



Quinoline-3-carboxamides

Figure 9.9 Pharmaceutically active compounds discovered from synthetic intermediates.

4 Finding a lead compound

4.4 Existing drugs

4.4.1 'Me too' drugs

1) Many companies use established drugs from their competitors as lead compounds in order to design a drug that gives them a foothold موطئ قدم in the same market area.
2) The aim is to modify the structure sufficiently such that
   1) it avoids patent restrictions,
   2) retains activity, and
   3) ideally has improved therapeutic properties.

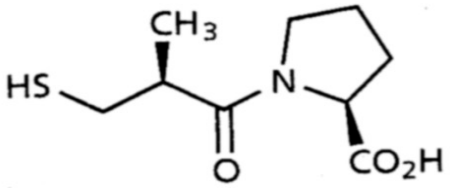
   For example, the antihypertensive drug captopril was used as a lead compound by various companies to produce their own antihypertensive agents (Fig. 9.10).
3) Although often disparaged بِـ اِسْتَخَفَّ as `me too' drugs, they can often offer improvements over the original drug. For example, modern penicillins are more selective, more potent, and more stable than the original penicillins.

I. Drug discovery-finding a lead

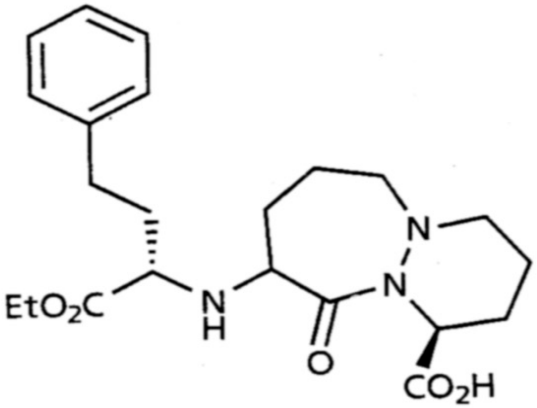
1. 4 Finding a lead compound

4.4 Existing drugs

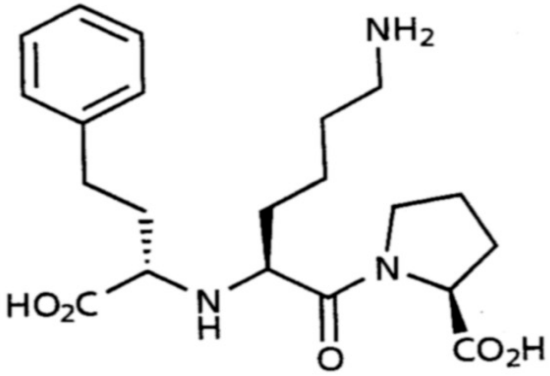
4.4.1 'Me too' drugs



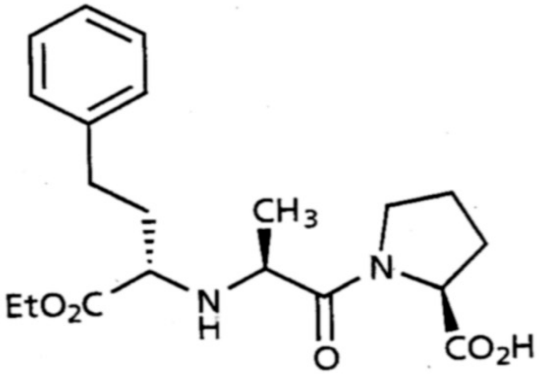
Captopril



Cilazapril
(Hoffmann-LaRoche)



Lisinopril
(Merck)



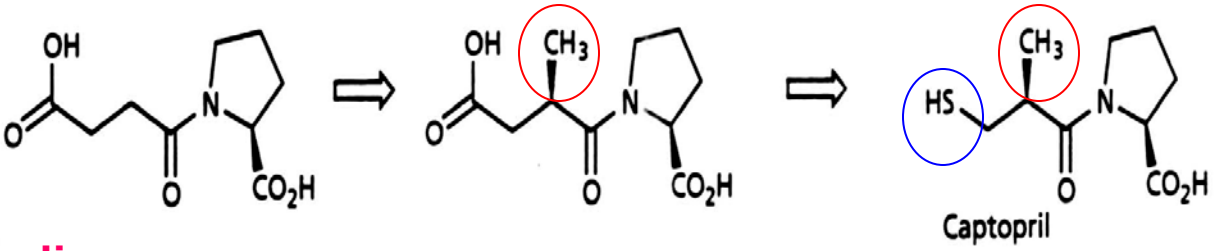
Enalapril
(Merck)

Figure 9.10 Captopril and 'me too' drugs.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3.2 Extension of the structure



Increased activity

succinyl proline

Figure 10.65 Development of captopril.

Extension strategies

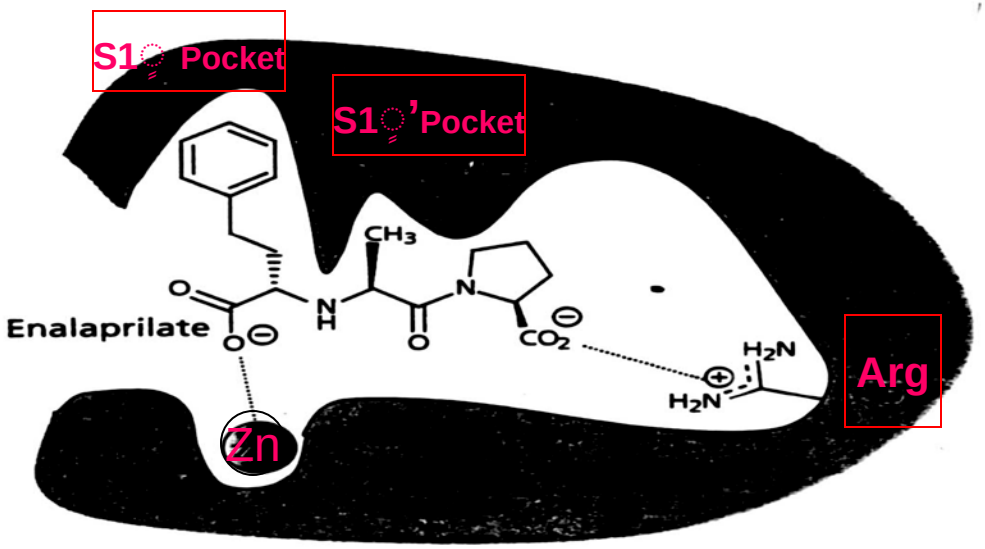


Figure 10.66 Enalaprilate.

binding characteristics using structure-based drug design.

4 Finding a lead compound

4.4 Existing drugs

4.4.2 Enhancing a side effect

- An existing drug may have a minor property or an undesirable side effect which might 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 :1) enhance the desired side effect and to 2) eliminate the 'major biological activity.

I. Drug discovery-finding a lead

4 Finding a lead compound

4.4 Existing drugs

4.4.2 Enhancing a side effect

- For example, most sulfonamides were used as antibacterial agents. However, some sulfonamides with antibacterial activity could not be used clinically because they had convulsive side effects brought on by hypoglycemia (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.

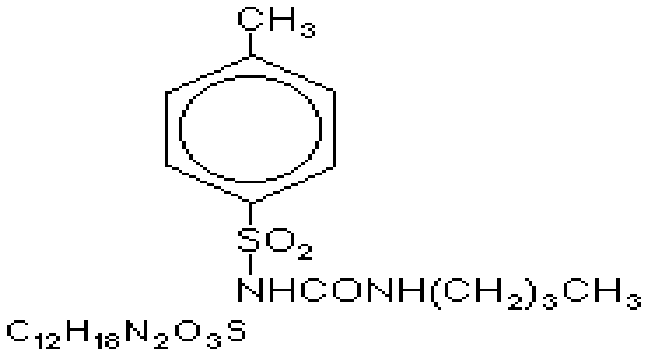
  This led to the antidiabetic agent tolbutamide (Fig. 9.11).

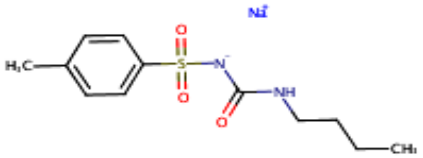
I. Drug discovery-finding a lead

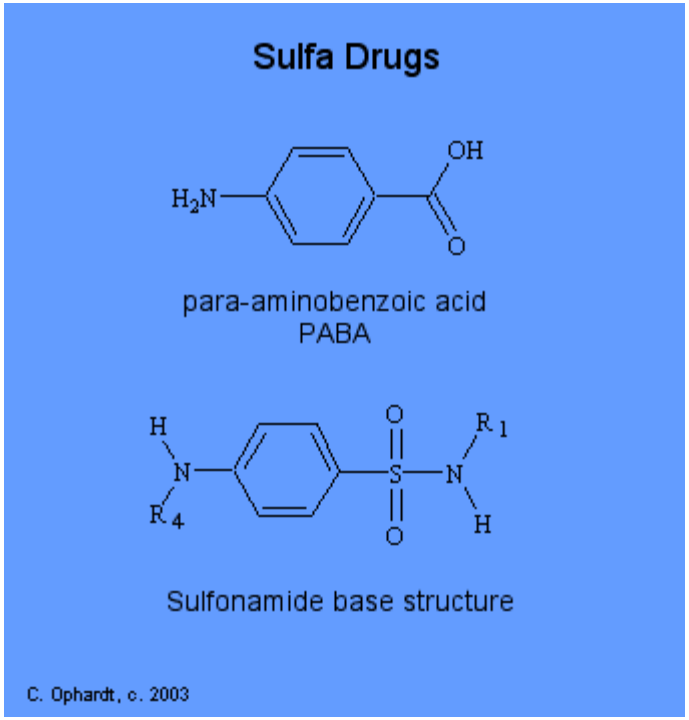
4 Finding a lead compound

4.4 Existing drugs

4.4.2 Enhancing a side effect







I. Drug discovery-finding a lead

1. 4 Finding a lead compound

4.4 Existing drugs

4.4.2 Enhancing aside 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) (Fig. 9.11) was originally designed as a vasodilator to treat angina and hypertension. During clinical trials, it was discovered 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.

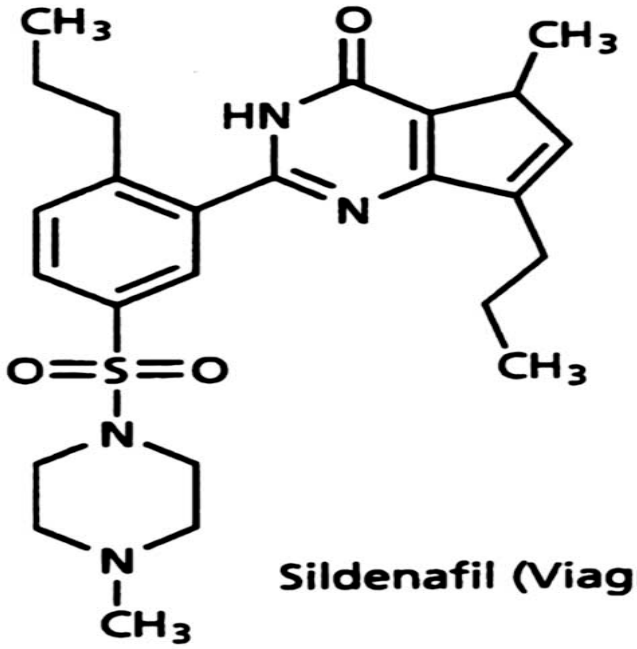
I. Drug discovery-finding a lead

4 Finding a lead compound

4.4 Existing drugs

4.4.2 Enhancing a side effect

Tolbutamide



Sildenafil (Viagra)

Figure 9.11 Tolbutamide and sildenafil (Viagra).

I. Drug discovery-finding a lead

4 Finding a lead compound

4.4 Existing drugs

4.4.2 Enhancing aside effect

BOX 9. 3 ENHANCING A SIDE EFFECT

Several drugs have been developed by enhancing the side effect of another drug.

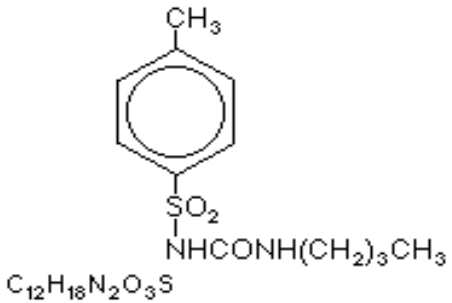
1- Chlorpromazine is used as a neuroleptic agent in psychiatry, but was developed from the antihistamine agent promethazine. This might appear an odd thing to do, but it is known that promethazine has sedative side effects and so medicinal chemists modified the structure to the effects at the expense of antihistamine activity.

I. Drug discovery-finding a lead

4 Finding a lead compound

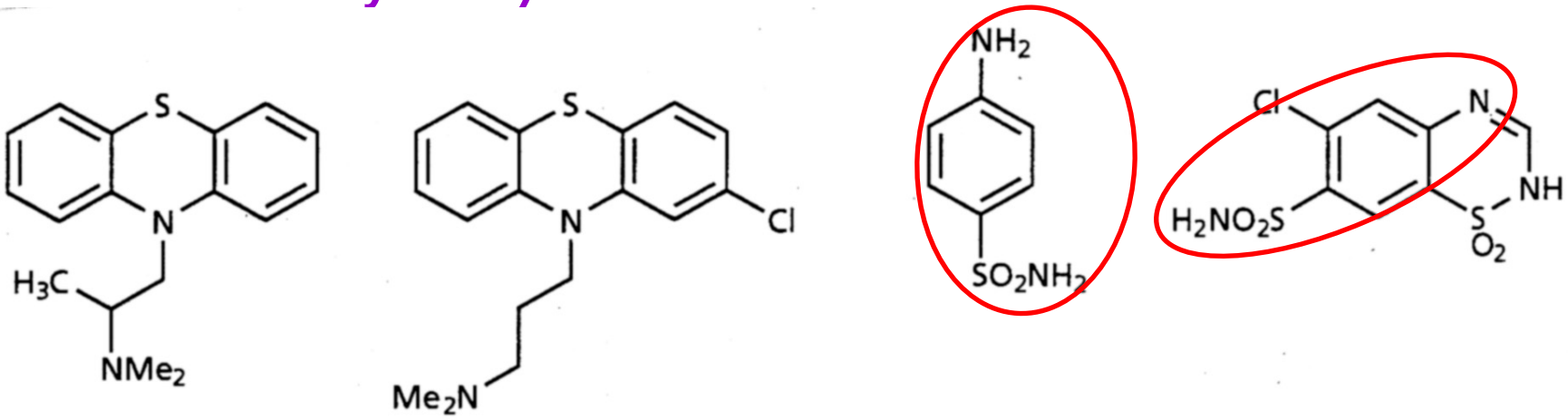
4.4 Existing drugs

4.4.2 Enhancing a side effect



BOX 9. 3 ENHANCING A SIDE EFFECT

2 - Similarly, the development of sulfonamide diuretics such as chlorothiazide arose from the observation that sulfanilamide has a diuretic effect in large doses (due to its action on an enzyme called carbonic anhydrase).



Drugs developed by enhancing a side effect.

I. Drug discovery-finding a lead

4 Finding a lead compound

4. 5 Starting from the natural ligand or modulator

4.5.1 Natural ligands for receptors

1) The natural ligand of a target receptor has sometimes been used as the lead compound:

- The natural neurotransmitters adrenaline and noradrenaline were the starting points for the development of adrenergic β-agonists such as salbutamol, (β2-agonist) , and dobutamine ((β1 –agonist)

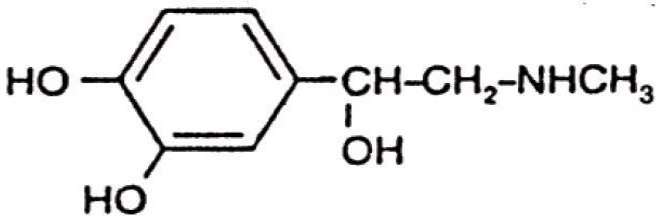
- 5-hydroxytryptamine (5-HT) was the starting point for the development of the 5-HT_1 agonist sumatriptan , is a medication used for the treatment of migraine headaches. (Fig. 9.12).

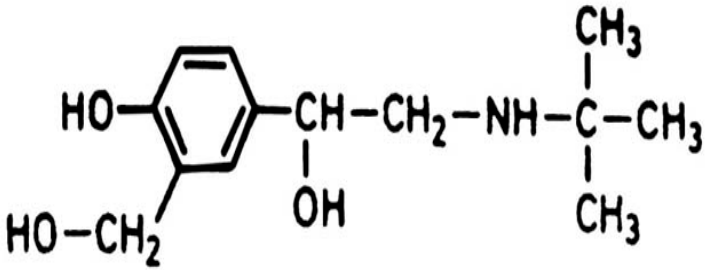
I. Drug discovery-finding a lead

4 Finding a lead compound

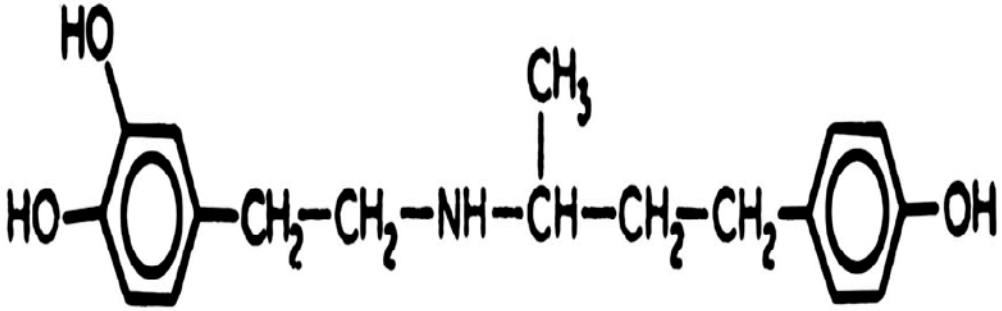
4. 5 Starting from the natural ligand

4.5.1 Natural ligands for receptors

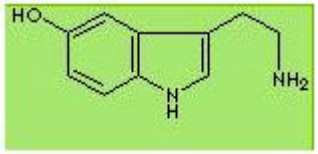




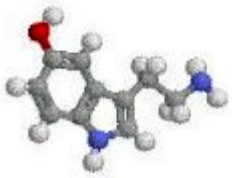
Salbutamol

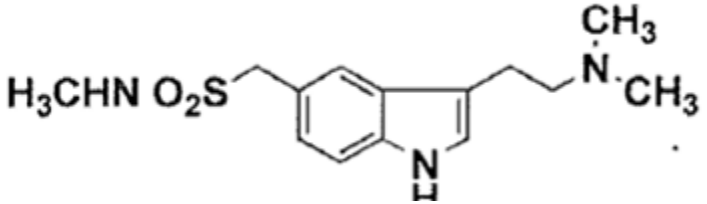


Dobutamine



Serotonin $C_{10}H_{12}N_2O$





sumatriptan

is a medication used for the treatment of migraine headaches.

I. Drug discovery-finding a lead

1. 4 Finding a lead compound

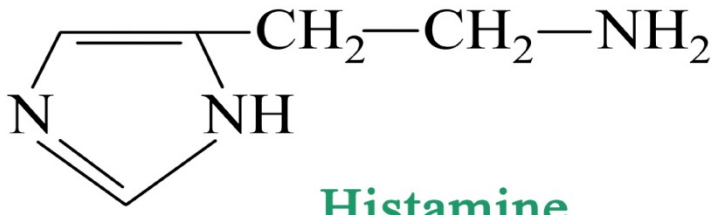
4.5 Starting from the natural ligand or modulator

4.5.1 Natural ligands for receptors

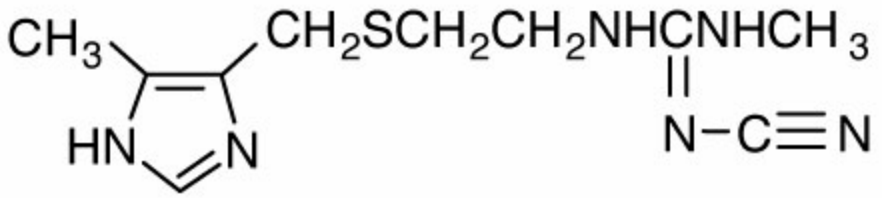
2) The natural ligand of a receptor can also be used as the lead compound in the design of an antagonist:

- histamine was used as the original lead compound in the development of the H_2 histamine antagonist cimetidine .

- Turning an agonist into an antagonist is frequently achieved by adding extra binding groups to the lead structure.



Histamine



cimetidine

I. Drug discovery-finding a lead

4 Finding a lead compound

4.5 Starting from the natural ligand or modulator

4.5.1 Natural ligands for receptors

3) Sometimes the natural ligand for a receptor is not known (an orphan receptor) and the search for it can be a major project in itself.

The identification of the opiate receptors for morphine led to a search for endogenous opiates (natural body painkillers) which eventually led to the discovery of endorphins, enkephalins, and endomorphins as the natural ligands and their use as lead compounds .

4 Finding a lead compound

4.5 Starting from the natural ligand or modulator

4.5.2 Natural modulators as lead compounds

1) Many receptors and enzymes are under allosteric control.

2) The natural or endogenous chemicals that exert this control (modulators) could also serve as lead compounds.

For example, the benzodiazepines are synthetic compounds that modulate the receptor for γ-aminobutyric acid (GABA) by binding to an allosteric binding site.

4 Finding a lead compound

4.5 Starting from the natural ligand or modulator

4.5.2 Natural modulators as lead compounds

The natural modulators for this allosteric site were not known at the time benzodiazepines were synthesized, but endogenous peptides called endozepines have since been discovered which bind to the same allosteric binding site and which may serve as lead compounds for novel drugs having the same activity as the benzodiazepines

4 Finding a lead compound

4.6 Combinatorial 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 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.**

- **Combinatorial science has developed so swiftly سَرِيعًا that it is almost a branch of chemistry in itself .**

4 Finding a lead compound

4.7 Computer-aided design

- 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 software programs can then be used to study the binding site, and to design molecules which will fit and bind to the *site-de* novo design.

- In some cases, the enzyme or receptor cannot be crystallized and so X-ray crystallography cannot be carried out. However, 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.

4 Finding a lead compound

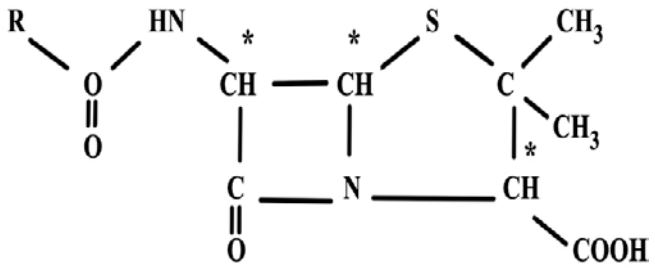
4.8 Serendipity and the prepared mind

- Frequently, lead compounds are found as a result of serendipity (i.e. chance). The discovery of cisplatin and penicillin are two such examples, but there are many more (see Box 9.5).

- Sometimes, the research carried out to improve a drug can have unexpected and beneficial spin offs. For example, propranolol and its analogues are effective β-blocking drugs (antagonists of β-adrenergic receptors) However, they are also lipophilic, which means that they can enter the central nervous system and cause side effects.

4 Finding a lead compound

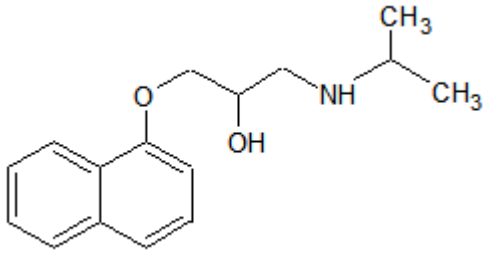
4.8 Serendipity and the prepared mind



penicillin

β-LACTAM ANTIBIOTIC

Atibacteria spectum : Gram positive(, ,S.aureus, Strepto , Pnemo.Gono , Minango)



antagonists of β-adrenergic receptors

Propranolol is a sympatholytic nonselective beta blocker. It is used to treat high blood pressure, a number of heart dysrhythmias,thyrotoxicosis, and essential tremors.[1]
It is used to prevent migraine headaches, and to prevent further heart problems in those with angina or previous heart attacks.[1] It comes in both oral and intravenous forms.[1]

I. Drug discovery-finding a lead

4 Finding a lead compound

4.8 Serendipity and the prepared mind

BOX 9.5 Example of serendipity

- mustard gas
- trinitrotoluene (TNT).
- Clonidine
- Imipramine
- sildenafil
- Chlorpromazine
- vincristine and vinblastine
- Ciclosporin A

I. Drug discovery-finding a lead

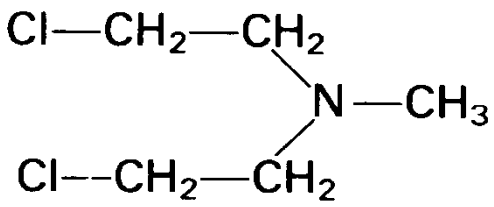
1. 4 Finding a lead compound

4.8 Serendipity and the prepared mind

BOX 9.5 Example of serendipity

1) During the Second World War, an American ship carrying mustard gas exploded in an Italian harbor. It was observed that many of the survivors who had inhaled the gas lost their natural defenses against microbes.

Further study showed that their white blood cells had been destroyed. It is perhaps hard to see how a drug that weakens the immune system could be useful. However, there is one disease where this is the case leukaemia.



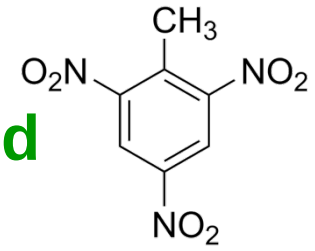
Nitrogen mustard

I. Drug discovery-finding a lead

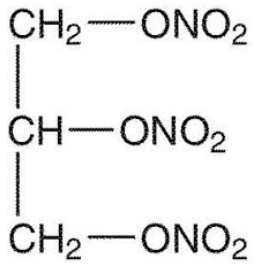
1. 4 Finding a lead compound

4.8 Serendipity and the prepared mind

BOX 9.5 Example of serendipity



TNT



nitroglycerine

2) Another example involved the explosives industry, where it was quite common for workers to suffer severe headaches.

These headaches resulted from dilatation of blood vessels in the brain, caused by handling trinitrotoluene (TNT).

Once again, it is hard to see how such drugs could be useful. Certainly, the dilatation of blood vessels in the brain may not be particularly beneficial, but dilating the blood vessels in the heart could be useful in cardiovascular medicine.

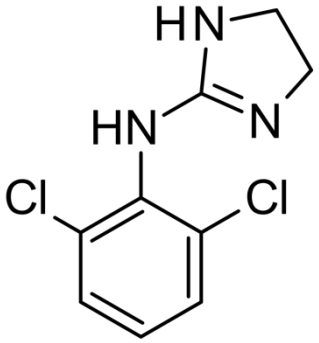
As a result, drugs were developed which dilated coronary blood vessels and alleviated the pain of angina (nitroglycerine).

I. Drug discovery-finding a lead

1. 4 Finding a lead compound

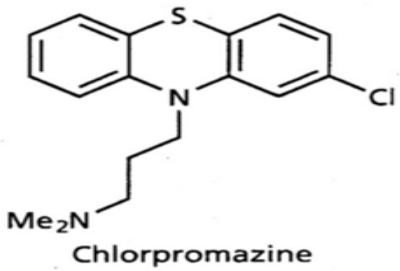
4.8 Serendipity and the prepared mind

BOX 9.5 Example of serendipity

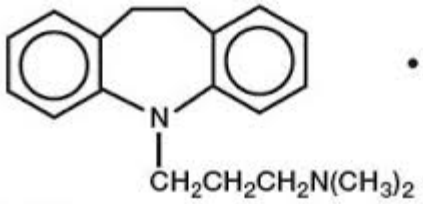


3) • **Clonidine was originally designed to be a nasal vasoconstrictor to be used in nasal drops and shaving soaps. Clinical trials revealed that is caused a marked fall in blood pressure and so it became an important anti hypertensive instead.**

4) • **Imipramine was synthesized as an analogue of chlorpromazine, and was initially to be used as an antipsychotic. However, it was found to alleviate depression and this led to the development of a series of compounds classified as the tricyclic antidepressants.**



Chlorpromazine



$C_{19}H_{24}N \cdot HCl$ M.W. 316.87

I. Drug discovery-finding a lead

1. 4 Finding a lead compound

4.8 Serendipity and the prepared mind

BOX 9.5 Example of serendipity

5) • **Aminoglutethimide** was prepared as a **potential antiepileptic** drug, but is now used as an **anticancer agent**

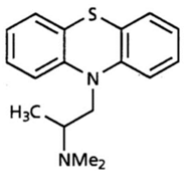
6) The **antiimpotence drug sildenafil** (Viagra) (Fig. 9.11) was discovered by chance from a project aimed at **developing a new heart drug.**

7) • **Iproniazid** (Fig. 9.9) was originally developed as an **antituberculosis** agent. Patients taking it proved remarkably **cheerful** مبتهجand this led to the drug becoming the lead compound for a series of **antidepressant drugs** known as the **monoamine oxidase inhibitors (MAOIs)** .

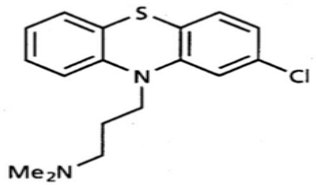
I. Drug discovery-finding a lead

1. 4 Finding a lead compound

4.8 Serendipity and the prepared mind



Promethazine



Chlorpromazine

BOX 9.5 Example of serendipity

8) • **Chlorpromazine** (Box 9.3) was synthesized as an **antihistamine** for possible use in preventing surgical shock, and was found to make patients **relaxed and unconcerned**. This led to the drug being tested in people with **manic depression** (Bipolar Disorder) where it was found **to have tranquillizing effects**, resulting in it being the first of the **neuroleptic drugs (major tranquillizers) used for schizophrenia.**

9) • In a similar vein, the alkaloids **vincristine** and **vinblastine** were discovered by chance when searching for compounds that **could lower blood sugar levels**. **Vincristine is used in the treatment of Hodgkin's disease.**

I. Drug discovery-finding a lead

1. 4 Finding a lead compound

4.8 Serendipity and the prepared mind

BOX 9.5 Example of serendipity

10) • **Ciclosporin A (Fig. 9.6) suppresses the immune system and is used during organ and bone marrow transplants to prevent the immune response rejecting the donor organs.**

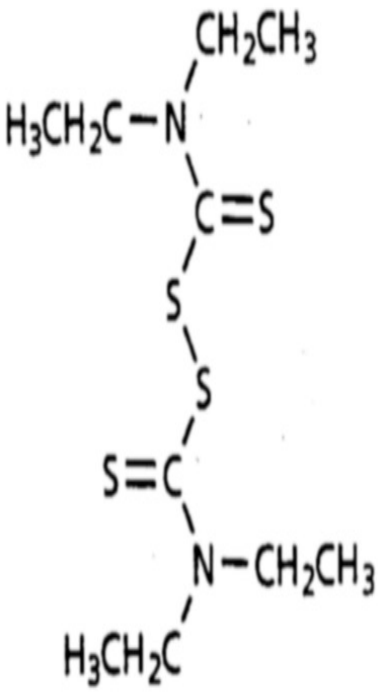
The compound was isolated from a soil sample as part of a study aimed at finding new antibiotics. Fortunately, the compounds were more generally screened and ciclosporin A's immunosuppressant properties were identified.

I. Drug discovery-finding a lead

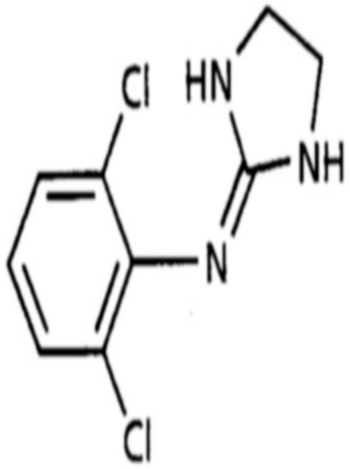
4 Finding a lead compound

4.8 Serendipity and the prepared mind

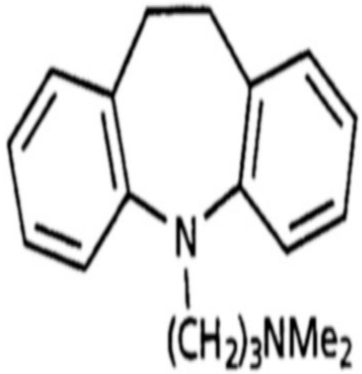
BOX 9.5 Example of serendipity



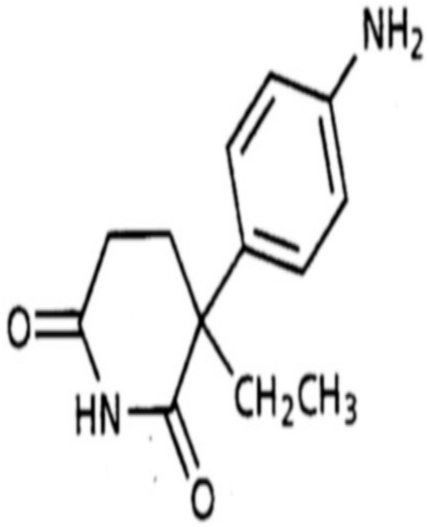
Disulfiram (Antabuse)



Clonidine



Imipramine



Aminoglutethimide

Drugs discovered by serendipity.

5 Isolation and purification

- If the lead compound (or active principle) is present in a mixture of other compounds, whether the mixture be from a natural source or from a combinatorial synthesis, it has to be isolated and purified.

- The ease with which the active principle can be isolated and purified depends very much on the: 1-structure, 2-stability, and 3- quantity of the compound. For example:

  Fleming recognized the antibiotic qualities of penicillin and its remarkable non-toxic nature to humans, but he disregarded it as a clinically useful drug because he was unable to purify it.

6 - Structure determination

- It is sometimes hard for present-day chemists to appreciate how difficult structure determinations were before the days of NMR and IR spectroscopy.

- A novel structure which may now take a week's work to determine would have provided two or three decades of work in the past.

  For example, the microanalysis of cholesterol was carried out in 1888 to get its molecular formula, but its chemical structure was not fully established until an X-ray crystallographic study was carried out in 1932.

I. Drug discovery-finding a lead

KEY POINTS

- A **lead compound** is a structure which shows a useful pharmacological activity and can act as the starting point for drug design.
- **Natural products** are a rich source of lead compounds. The agent responsible for the biological activity of a natural extract is known as the **active principle**.
- **Lead compounds** have been **isolated** from **plants, trees, microorganisms, animals, venoms, and toxins**. A study of **medical folklore** indicates plants and herbs which may contain novel lead compounds.
- **Lead compounds** can be found by **screening synthetic compounds** obtained from combinatorial syntheses and other sources.

I. Drug discovery-finding a lead

KEY POINTS

- The natural ligand, substrate, product, or modulator for a particular target can act as a lead compound.
- The ability to crystallize a molecular target allows the use of X-ray crystallography and molecular modelling to design lead compounds which will fit the relevant binding site.
- Serendipity has played a role in the discovery of new lead compounds.
- A knowledge of an existing drug's pharmacophore allows the computerized searching of structural databases to identify possible new lead compounds which share that pharmacophore.

The end

I. Drug discovery-finding a lead

Drug development phases

Clinical trials are designed to:

- determine safety and tolerance in man;
- pharmacokinetics (what the body does with the drug);
- bioavailability for a range of doses;
- determine the pharmacological profile.

The main phases of pre-clinical and clinical trials are:

Pre-clinical	Animal studies. Submission of "Investigational New Drug" application to government bodies such as US FDA.
Phase I	Normal, healthy human volunteers.
Phase II	To evaluate safety and efficacy of drug in patients.
Phase III	Large patient number study to establish efficacy *versus* a placebo or comparator compound.
Phase IV	Long-term surveillance / monitoring of adverse reactions.

I. Drug discovery-finding a lead

QUESTIONS

1-What is meant by target specificity and selectivity? Why is it important?

lead compound?

2-What are the advantages and disadvantages of natural products as lead compounds?

3-Fungi have been a richer source of antibacterial agents than bacteria. Suggest why this might be so.

4-Scuba divers and snorkellers are advised not to touch coral. Why do you think this might be? Why might it be of interest to medicinal chemists?

5-You are employed as a medicinal chemist and have been asked to initiate a research programme aimed at finding a drug which will prevent a novel tyrosine kinase receptor from functioning. There are no known lead compounds that have this property. What approaches can you make to establish a lead compound? (Consult section 6.7 to find out more about protein kinase receptors.)

I. Drug discovery-finding a lead

6 - A study was set up to look for agents that would inhibit the kinase active site of the epidermal growth factor receptor (section 6.7). Three assay methods were used: an assay carried out on a genetically engineered form of the protein that was water soluble and contained the kinase active site; a cell assay that measured total tyrosine phosphorylation in the presence of epidermal growth factor; and an in vivo study on mice that had tumours grafted onto their backs. How do you think these assays were carried out to measure the effect of an inhibitor? Why do you think three assays were necessary? What sort of information did they provide?