Medicinal Chemistry

- Medicinal chemistry is the discipline concerned with discovery and development of medicinal agents as well as with determining the influence of chemical structure on biological activity.
- It occupies a strategic position at the interface of chemistry and biology.

Drug Discovery & Development

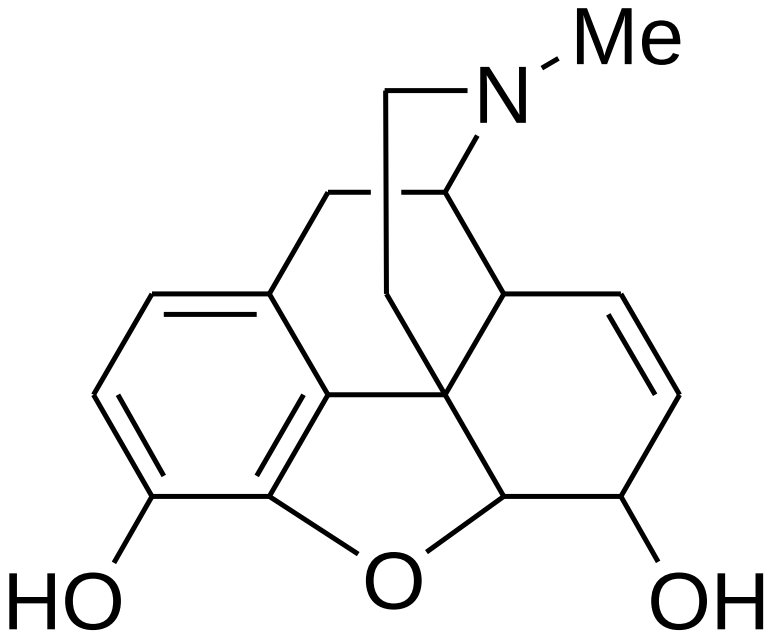
- The process of establishing a new pharmaceutical is exceedingly complex and involves the talents of people from a variety of disciplines, including chemistry, biochemistry, molecular pharmacology, pharmaceutics, and medicine.
- Medicinal chemistry is concerned mainly with the organic, analytical, and biochemical aspects of this process, but its scientists must interact productively with those in other disciplines.

Why Do Medicinal Chemists Have to Develop new Drugs?

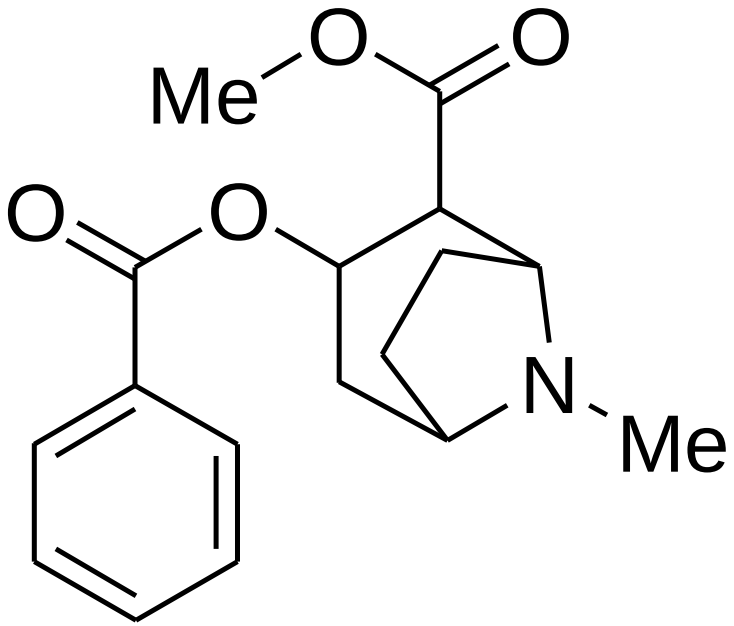
- To increase activity.
- To reduce side-effects.
- To provide easy and efficient administration to the patient.
- Ease of synthesis.

Drug Discovery & Development – The Past

- Medicines, usually derived from plants and other natural sources, have been used by humans for thousands of years to alleviate pain, diarrhea, infection, and various other diseases.
- Before the twentieth century these medicines consisted mainly of herbs and potions.
- It was not until the mid-nineteenth century that the first efforts were made to isolate and purify the chemical compounds, responsible for the medical properties, from these mixtures.



morphine (opium)



cocaine (coca)

- These natural products sparked off a major synthetic effort in which chemists made literally thousands of analogues in an attempt to improve on what nature had provided.
- Much of this work was carried out on a trial and error basis, but the results obtained revealed general principles behind drug design.
- The mechanism by which a drug worked at the molecular level was rarely understood and drug research very much focused on what is known as the lead compound, the active principle isolated from the plant.

Drug discovery & Development – The Present

- Rapid advances in the biological sciences have resulted in a much better understanding of how the body functions at the cellular and molecular levels.
- As a result, most research projects in the pharmaceutical industry now begin by identifying a suitable target in the body and designing a drug to interact with that target.

Disease → Drug target → Bioassay → Lead compound →

Isolate & purify → Structure → SAR → Pharmacophore →

Analogues → Pharmacokinetic → Metabolism → Toxicity

→ Manufacturing → Clinical trial → Market

Choose a Disease

- It is a matter of pharmaceutical company's strategists.

  1- Medical factors: Diseases where there is a need for new and/or improved drug.

  2- Economical factors: A good financial return.

- Research projects are first world-oriented.
- Cancer, migraine, ulcer, depression, CV diseases, etc.

Choose a Drug Target

- An understanding of which enzymes or receptors or nucleic acid are involved in a particular disease state is clearly important.
- Medicinal research team would identify whether agonists or antagonists should be designed for a particular enzyme

Identify a Bioassay

- The test should be simple, quick, and relevant since a large number of compounds usually need to be analyzed.
- Human testing is not possible at such an early stage.
- The test has to be done *in vitro* (i.e. on isolated cells, tissues, enzymes, or receptors) or *in vivo* (on animals).

Find a Lead Compound

- A compound which shows the desired pharmaceutical activity.
- The lead compound provides a start for the drug development process.
- The level of activity may not be very great and there may be undesirable side-effects.
- There are many ways in which a lead compound might be discovered.

Ways to Find a Lead Compound

- Screening of natural materials.
- Medical folklore.
- Screening of synthetic banks.
- Existing drugs.
- Starting from the natural ligand.
- Combinatorial synthesis.
- Computer-aided design.
- Serendipity and the prepared mind.

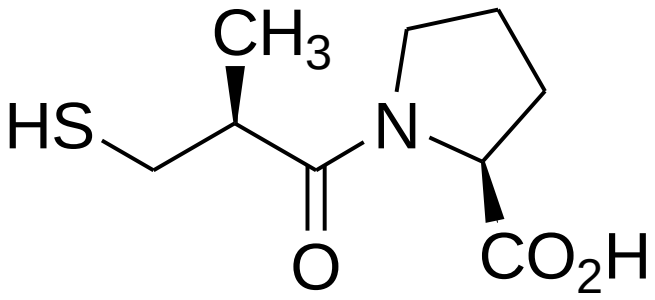
Discovering Lead Compounds from an Existing Drugs

- Me too drugs:

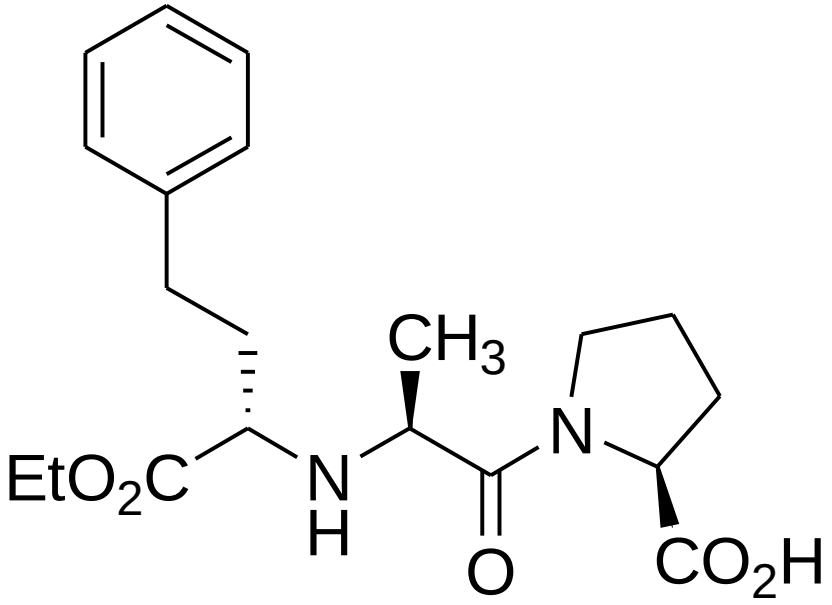
  Many companies use established drugs from their competitors as lead compounds to design a drug which gives them a foothold in the same market area.

- Enhancing a side-effect:

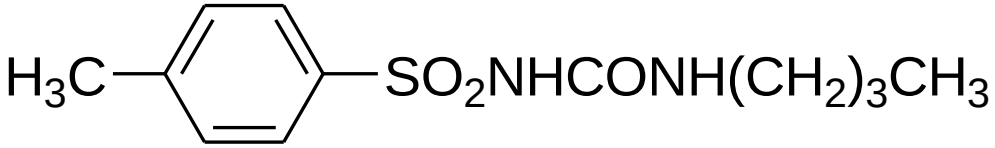
  A drug could act as a lead compound based on its side-effects.



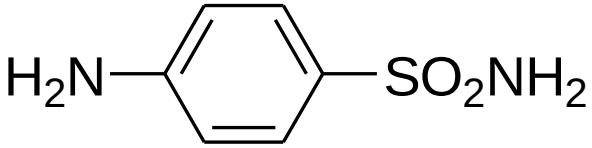
captopril
(Squibb)



Enalapril
(Merck)



tolbutamide



sulphanilamide

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Discovering Lead Compounds Starting from a Natural Ligand

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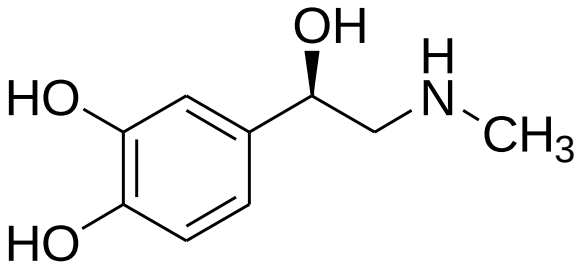
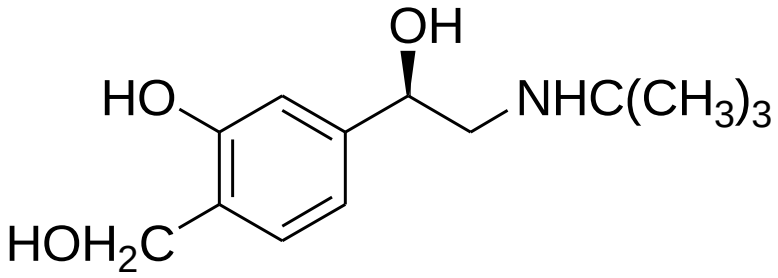


adrenaline



salbutamol

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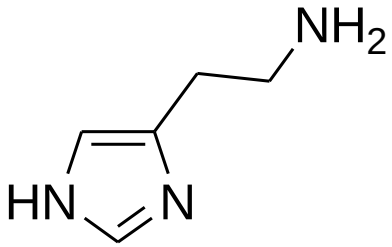
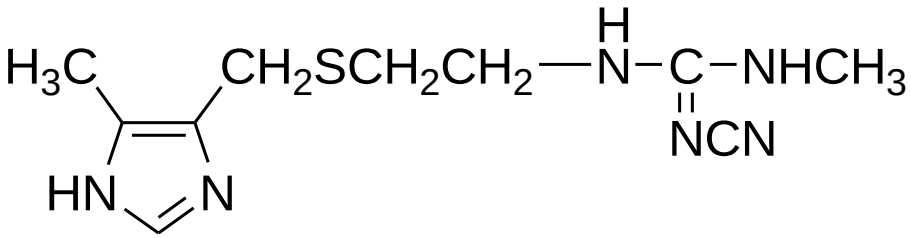


histamine



cimetidine

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Isolate & Purify the Lead Compound (if necessary)

- Isolation and purification of the lead compound (or active principle) is necessary if it is present in a mixture of other compounds.
- The ease with which the active principle can be isolated and purified depends very much on the structure, stability, and quantity of the compound.

Determine the Structure of the Lead Compound

- The most useful analytical techniques are X-ray crystallography, NMR, IR, and MSS.

Identify Structure-Activity Relationships

- To discover which parts of the molecule are important to biological activity and which are not.
- The chemist makes a selected number of compounds, which vary slightly from the original molecule, and studies what effect this has on the biological activity.

Identify the Pharmacophore

- The pharmacophore summarizes the important functional groups which are required for activity and their relative positions in space with respect to each other.

Analogues Synthesis: Target-Oriented Drug Design

- Stronger drug-target interactions should increase the activity of the drug while an increase in target selectivity will lower side-effects.
- Lead compounds usually have serious side-effects and there is an advantage in finding analogues which lack them.
- Synthesis of analogues of the lead compound which contain the same pharmacophore is important.

Improve Pharmacokinetic Properties (Pharmacokinetic drug design)

- Some of the most active drugs discovered *in vitro* show no activity at all *in vivo*.
- A clinically useful drug has to travel through the body to reach its target.
- There are many barriers and hurdles which can prevent a drug reaching its target.
- Pharmacokinetic drug design concentrates on designing drugs to overcome these barriers.

Study Drug Metabolism

- When drugs enter the body, they are attacked by a whole range of metabolic enzymes, mostly in the liver, whose role is to degrade or modify foreign structures such that they can be excreted.
- As a result most drugs undergo some form of metabolic reaction, resulting in modified structures known as metabolites.
- Drugs should be tested on animals and humans to see what metabolites are formed. This is safety issue, since it is important to ensure that no toxic metabolites are formed.

Study Drug Metabolism

- Drug metabolism studies can sometimes be useful in drug design. On several occasions it has been found that a drug which is active *in vivo* is inactive *in vitro*. This is often a sign that the structure is not really active at all, but is being converted to the active drug by metabolism.

Test for Toxicity

- Before the drug moves on to clinical trials it is tested for toxicity.

Design a Manufacturing Process

- The industrial synthesis of a drug should be efficient and economic.
- If a choice must be made between two drugs where one is slightly less active than the other but is easier to synthesize, then the less active structure may well be chosen for clinical trials and further development.

Carry out Clinical Trials

- Clinical trials involve testing the drug on volunteers and patients.
- Many promising drug candidates fail this final hurdle and, if this happens, further analogues may need to be prepared before a clinically acceptable drug is achieved.
- There are four phases of clinical trials

Clinical Trials: Phase I Studies

- Carried on healthy volunteers to test whether the drug has the effect claimed.
- Tests are also carried out to test drug's potency, pharmacokinetics, and side-effects.

Clinical Trials: Phase II Studies

- The drug is tested on small group of patients to see if it has any effect and to find out what dose levels should be used.

Clinical Trials: Phase III Studies

- The drug is tested on a much larger sample of patients and compared with other available treatments.
- Alternatively, they may be compared with a placebo (i.e. a preparation which has no effect at all).

Clinical Trials: Phase IV Studies

- The drug is now placed on the market and can be prescribed.
- However, the drug is still monitored for its effectiveness and for any unexpected side-effects.

Conclusion

- Many of these stages run concurrently and are dependent on each other.
- For example, drug metabolism studies, toxicity testing and the development of a large scale synthesis are usually carried out in parallel.
- Even so, the discovery and development of a new drug can take 10 years or more, involve the synthesis of over 10000 compounds and cost in the region of 360 million USD.