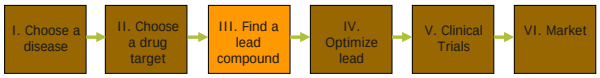
Drug Discovery

- General plan:



Finding the Lead

Screening Natural Products

- Plants, microbes, the marine world, and animals, all provide a rich source of structurally complex natural products.
- It is necessary to have a quick assay for the desired biological activity and to be able to separate the bioactive compound from the other inactive substances
- Lastly, a structural determination will need to be made

Finding the Lead

Screening synthetic banks

- Pharmaceutical companies have prepared thousands of compounds
- These are stored (in the freezer!), cataloged and screened on new targets as these new targets are identified

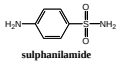
Finding the Lead

Using Someone Else's Lead

- Design structure which is similar to existing lead, but different enough to avoid patent restrictions.
- Sometimes this can lead to dramatic improvements in biological activity and pharmacokinetic profile.
  - e.g. modern penicillins are much better drugs than original discovery.

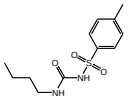
Finding the Lead

Enhance a side effect



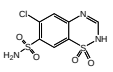
sulphanilamide

(an antibacterial with the side effect of lowering glucose levels in the blood and also diuretic activity)



tolbutamide

(a compound which has been optimized to only lower blood glucose levels. Useful in the treatment of Type II diabetes.)

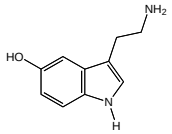


Chlorothiazide

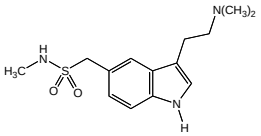
(a compound which has been optimized to only display diuretic activity.)

Finding the Lead

Use structural similarity to a natural ligand



5-Hydroxytryptamine (5-HT)
Serotonin (a natural neurotransmitter synthesized in certain neurons in the CNS)



Sumatriptan (Imitrex)
Used to treat migrain headaches known to be a 5-HT_1 agonist

Finding the Lead

Computer-Assisted Drug Design

- If one knows the precise molecular structure of the target (enzyme or receptor), then one can use a computer to design a perfectly-fitting ligand.
- Drawbacks: Most commercially available programs do not allow conformational movement in the target (as the ligand is being designed and/or docked into the active site). Thus, most programs are somewhat inaccurate representations of reality.

Finding the Lead

Serendipity: a chance occurrence

- Must be accompanied by an experimentalist who understands the "big picture" (and is not solely focused on his/her immediate research goal), who has an open mind toward unexpected results, and who has the ability to use deductive logic in the explanation of such results.
- Example: Penicillin discovery

Structure Activity Relationships (SAR)

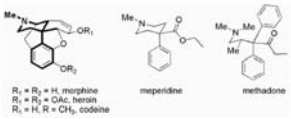
- Once the structure of lead compound is known, the medicinal chemist moves on to study its SAR.
- The aim is to discover which parts of the molecule are important to biological activity and which are not.
- X-ray crystallography and NMR can be used to study and identify important binding interactions between drug and active site.
- SAR is synthesizing compounds, where one particular functional group of the molecule is removed or altered.
- In this way it is possible to find out which groups are essential and which are not for biological effect.

Structure Activity Relationships (SAR)

- This involves testing all analogues for biological activity and comparing them with the original compound.
- If an analogue shows a significant lower activity, then the group that has been modified must be important.
- If the activity remain similar, then the group is not essential.
- It may be possible to modify some lead compounds directly to the required analogues and other analogues may be prepared by total synthesis.

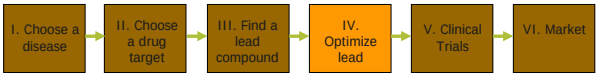
Identification of a Pharmacophore

- We have defined a lead compound as "a compound from a series of related compounds……". The question is therefore posed what are the essential structural elements for biological activity?
- A pharmacophore is "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity". A pharmacophore may not be identified until many analogues have been made and tested. But which ones to make?



Drug Discovery

- General plan:



Optimize Lead Compound

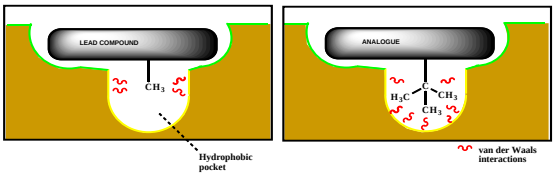
- Drug optimization aims to maximize the interactions of a drug with its target binding site in order to improve activity, selectivity and to minimize side effects.
- Designing a drug that can be synthesized efficiently and cheaply is another priority.
- The aim of drug optimization can be achieved by different strategies or approaches on the lead compound SAR, such as;

Optimize Lead Compound

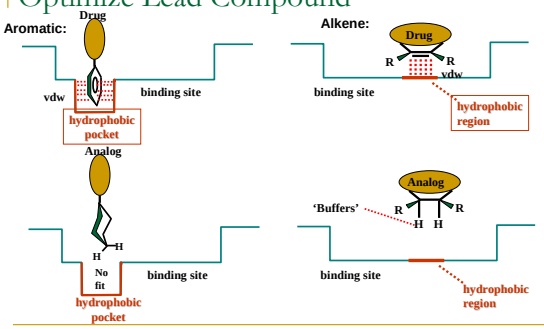
- The aim of drug optimization can be achieved by different strategies or approaches on the lead compound SAR, such as
  - Variation of substituents
    - alkyl and aromatic substitution
  - Extension of structure
    - chain extension/contraction, ring expansion /contraction
  - Ring variation
  - Ring fusion
  - Isosteres and bioisosteres
  - Simplification of the structure
  - Rigidification of the structure
  - Conformational blockers

Optimize Lead Compound

Variation of alkyl substituents



Optimize Lead Compound



Optimize Lead Compound

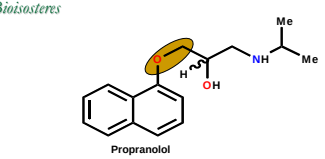
Isosteres and Bioisosteres

Isosteres and Bioisosteres

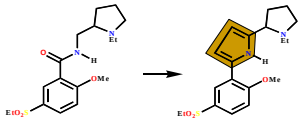
- The isostere concept was formulated by Irving Langmuir in 1919, and later modified by Grimm. Friedrich Erlenmeyer extended the concept to biological systems in 1932.
- Classical isosteres are defined as being atoms, ions and molecules that had identical outer shells of electrons,
  - Examples: N_2 and CO, N_2O and CO_2, N_3 and NCO
- This definition has now been broadened to include groups that produce compounds that can sometimes have similar biological activities.
- A biological compound containing an isostere is called a bioisostere. This is frequently used in drug design:
  - the bioisostere will still be recognized and accepted by the body, but its functions there will be altered as compared to the parent molecule.

Optimize Lead Compound

Isosteres and Bioisosteres



Propranolol



Sultopride DU 122290

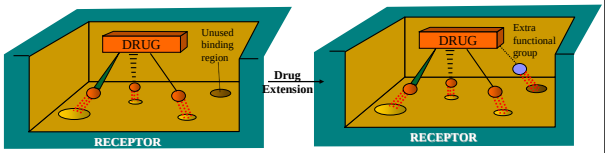
Optimize Lead Compound

Optimizing Access to the target

- The compound with the best binding interaction is not necessarily the best drug to use in medicine.
- The drug needs to pass through many barriers to reach its target in the body.
- There are many ways to make the drug to reach its target such as linking the drug to polymers or antibodies or encapsulating it within a polymeric carrier.
- Thus, the aim is to design drugs that will be absorbed into the blood supply (absorption) and will reach their target efficiently (distribution) and be stable enough to survive the journey (metabolism) and will be eliminated in a reasonable period of time (elimination).
- In other words, designing a drug with optimum pharmacokinetics can be achieved by different strategies.

Optimize Lead Compound

Extension of structure



Optimize Lead Compound

Extension of structure

Adrenaline

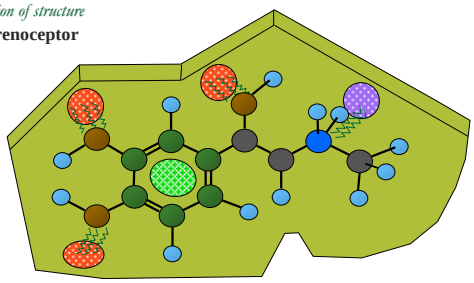
Salbutamol (Ventolin)
(Anti-asthmatic)

Propranolol
(β-Blocker)

Optimize Lead Compound

Extension of structure

β-Adrenoceptor

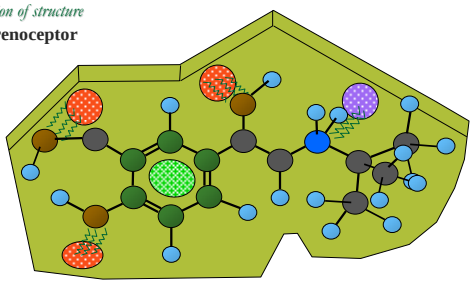


ADRENALINE

Optimize Lead Compound

Extension of structure

β-Adrenoceptor

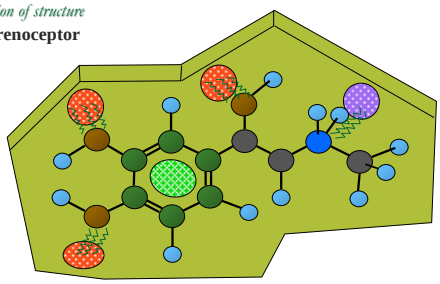


SALBUTAMOL

Optimize Lead Compound

Extension of structure

α-Adrenoceptor

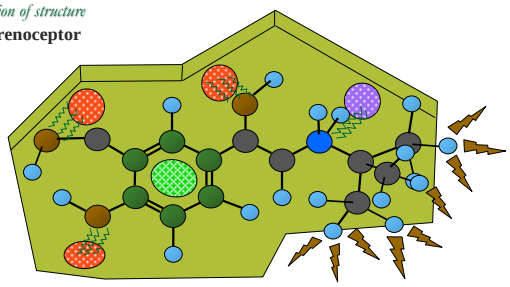


ADRENALINE

Optimize Lead Compound

Extension of structure

α-Adrenoceptor

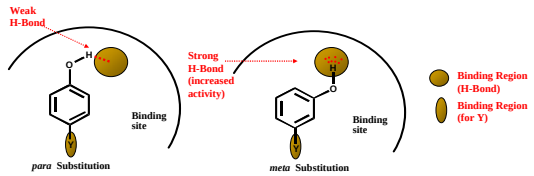


SALBUTAMOL

Optimize Lead Compound

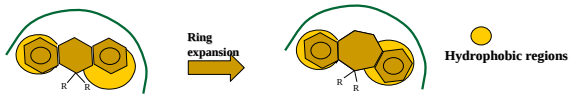
Variation of Ring Size and Structure

Change in substitution pattern

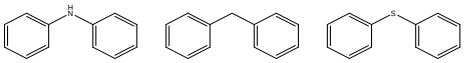


Optimize Lead Compound

Variation of Ring Size and Structure

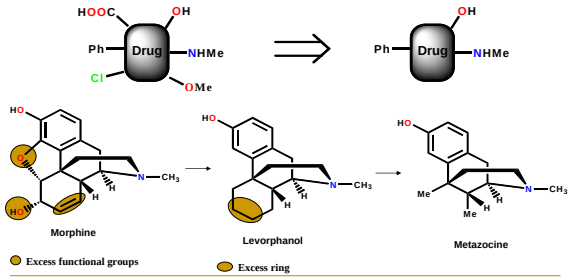


Variation in ring structure



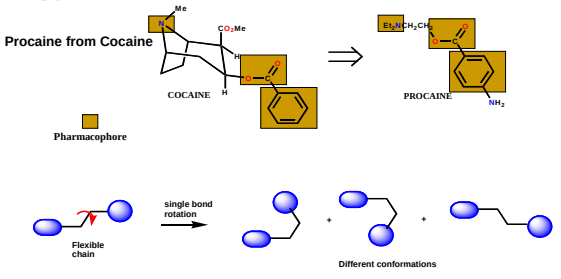
Optimize Lead Compound

Simplification



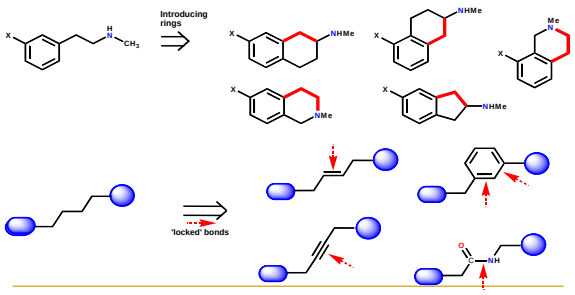
Optimize Lead Compound

Simplification



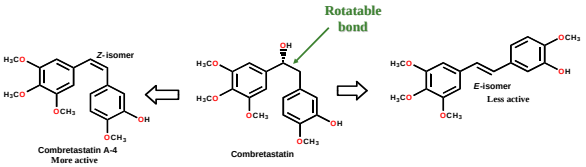
Optimize Lead Compound

Rigidification



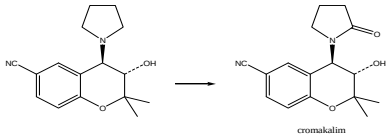
Optimize Lead Compound

Rigidification



Problems to Consider

- Pharmacokinetics
- Metabolism
- Prodrugs



- Synthesis/Manufacturing process

Metabolism of Drugs

There are two important aspects in drug design and drug strategies to improve :

- **Pharmacodynamics properties**: to optimize the interaction of the drug with its target.
- **Pharmacokinetics properties**: to improve the drug's ability to reach its target & to have acceptable lifetime.

- Pharmacodynamics and pharmacokinetics should have equal priority in influencing which strategies are used and which analogues are synthesized.

Metabolism of Drugs

- The body regards drugs as foreign substances, not produced naturally.
- Sometimes such substances are referred to as “xenobiotics”
- Body has “goal” of removing such xenobiotics from system by excretion in the urine
- The kidney is set up to allow polar substances to escape in the urine, so the body tries to chemically transform the drugs into more polar structures.

Metabolism of Drugs

- **Phase 1** Metabolism involves the conversion of nonpolar bonds (eg C-H bonds) to more polar bonds (eg C-OH bonds).
- A key enzyme is the cytochrome P450 system, which catalyzes this reaction:

$$RH + O_2 + 2H^+ + 2e^- \rightarrow ROH + H_2O$$

Metabolism of Drugs

- **Phase II** metabolism links the drug to still more polar molecules to render them even more easy to excrete