MEDICINAL CHEMISTRY II
DRUG Discovery and Development

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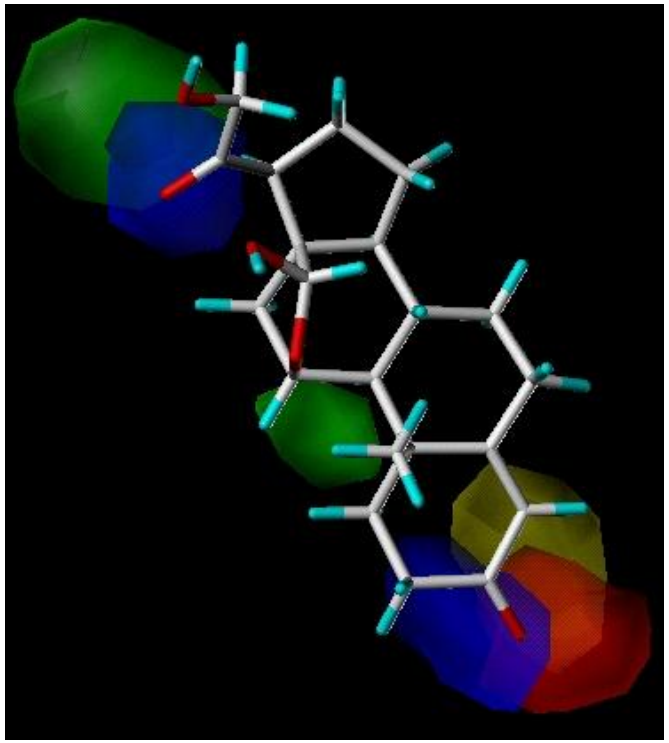


Dr: Abulsalam Alsubari
2019-2020

Learning outcomes

At the end of this module, student will be able to:
1-Have the knowledge and understand the principles of drug discovery and development .
2-Identify the different sources of lead compound.
2-Identify the method of optimization of lead compound to become drug.
4- Explain the relationship between the chemical structure (actives groups) and activity.
5- Explain the different reaction between the functional groups during drug preparation.
6.Identify the antibiotics discovery and development
7.Identify the sex hormone discovery and development
8. Identify the cardiovascular drugs discovery and development

Student assessment methods and references

- **Mid term exam 20 %**
- **Practical exam 30%**
- **Final exam 50%**

Total 100%

List of references

1. **Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry 11th ed. Lippincott, Williams & Wilkins ed.**
2. **Foye's Principles of Medicinal Chemistry. . Blundell T., 'Structure-based Drug Design', Nature, 384, 23-26,1996.**
3. **2. Kenny B.A. et al. The Application of High Throughput Screening to Novel Lead Discovery, Prog. Drug Res., 41 : 246-269, 1998.**
4. **1993.**
5. **DA and Lemke T.L. (Eds.), Lippincot Willams & Wilkins, New York, 5th edn., 2002.**
6. **5. Wolff M.E. (Ed.) Medicinal Chemistry and Drug Discovery,John Wiley & Sons, New York, 5th edn.,** 1995.

Content

- Definition of Medicinal chemistry
- Drug discovery and development in the past
- Drug discovery and development in the present
- Basic terms used in pharmaceutical chemistry
- How do drugs work?
- **Drug Discovery: finding a lead compound)**
  - lead definition
  - Sources of lead compound
  - Properties of lead compound
  - Isolation and purification of lead compound
  - Structure determination of lead compound

Content

- **Drug design optimization process**
  - Identify structure-activity relationships(SARs).
  - Identify the pharmacophore
  - Improve lead target interaction(pharmcodynamic)
  - Improve pharmacokinetic properties
- **Drug Development**
  - Design a manufacturing process
- Antibiotic discovery and development.
- Sex Hormones discovery and development
- cardiovascular drugs discovery and development

❑ Definition of Medicinal chemistry

is the science, which deals with the discovery , design and development of new drugs.

❑ Drug discovery and development in the past

For several thousand years,

- man has used herbs and potions as medicines.

At the mid-nineteenth century

- isolate and purify the active principles of these remedies . The success of these efforts led to the birth of many of pharmaceutical companies we know today.

Since then

- a large variety of biologically active compounds have been obtained and their structures determined (e.g. morphine from opium, cocaine from coca leaves, quinine from the bark of the cinchona tree).and became the lead compounds for a major synthetic drugs analogues.

❑ Drug discovery and development in the present

Rapid advance in the biological sciences

- understanding of the structure and the function of the target or receptors as well as the mechanism by which it interacts with drug.

As a result ,

- Most research projects in the pharmaceutical industry or university sector now begin by identifying a suitable target in the body and designing a drug to interact with that target.
- Generally, we can identify the following stages in drug discover, design and development.

Drug discovery and development in the present

Drug discovery

- Choose a disease
- Identify a therapeutic target in that pathway (e.g gene, key enzyme, receptor, ion-channel, nuclear receptor)
- Find a lead compound
- Isolate and purify the lead compound
- Determine the structure of the lead compound

Drug design

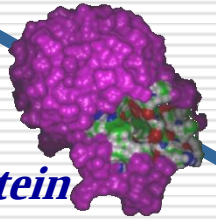
- Identify structure-activity relationships(SARs).
- Identify the pharmacophore
- Improve lead target interaction(pharmcodynamic)
- Improve pharmacokinetic properties

Drug Development

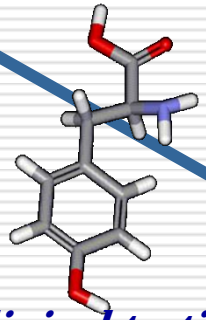
- Patent the drug
- Carry out preclinical trials (ADME)on animal
- Design a manufacturing process for bulk production
- Carry out clinical trials(on human)
- Register and market the drug
- Make money

Drug Discovery & Development

Identify disease



Isolate protein involved in disease (2-5 years)



Find a lead effective against disease protein (2-5 years)

Preclinical testing (1-3 years)

Scale-up

Human clinical trials (2-10 years)

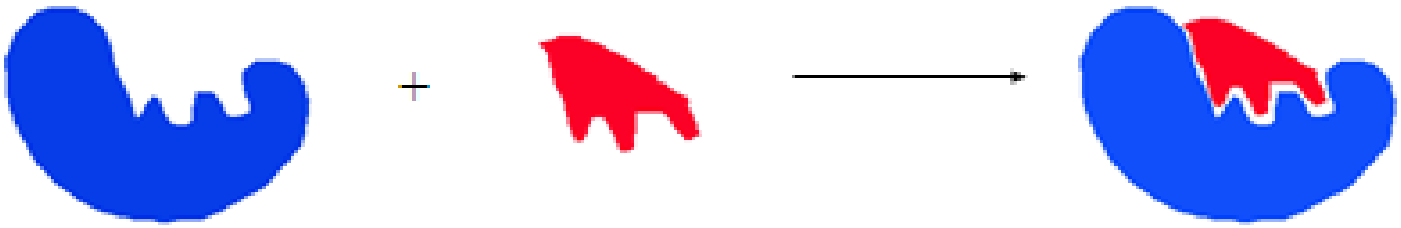
Formulation

FDA approval (2-3 years)

Basic terms used in pharmaceutical chemistry

- **Target** : bio molecule interacting with the drug (mostly protein)
- **Binding brocket** or active site: part of the target appropriate to bind a small ligand(pharmacophore).
- **Pharmacophore** : apart of a molecule that is recognized at a receptor site and is responsible for that molecules' biological activity.
- **Lead compound** : Base molecular structural motif of developed drug
- **Drug** : after success in clinical trial and approved by FDA
- **Structure activity relationship**: a relationship between the quantity of the drug(its structure) that binds to the active site and the biological activity.
- **Bioavailability** : Availability of compound in site of target in necessary concentration.

How Drugs Work



Receptor + Drug → Receptor-Drug complex

Lock-and-key model

The Lock - Active Site of Enzyme/Receptor

The Key - the Drug

Biological response is altered OR shut down

❑ Drug Discovery: (finding a lead compound)

- Once a target and testing system have been chosen, the next stage is to find a lead compound.
- A lead compound is a structure which shows a useful pharmacological activity but have some undesirable properties as low activity and side effects and need to optimized and developed to become safe drug.
- There are various ways in which a lead compound might be discovered as described in the following :

Sources of leads compounds

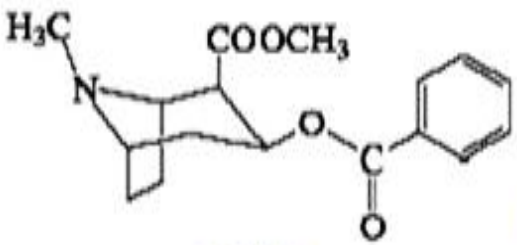
1. Plant sources.

Example ; Morphine, cocaine, digoxin, quinine, reserpine, ergotamine, ephedrine, colchicine etc. are still a part of standard therapy. Most of these don't have any synthetic substitutes.

Sources of leads compounds

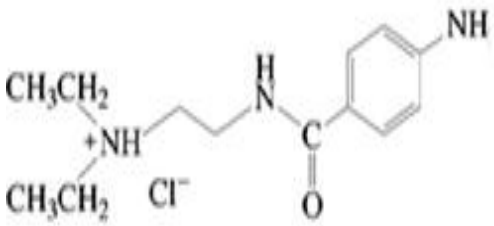
Example of Plant sources.
Cocaine disadvantage

- **Dependence**
- **Complex structure difficult to synthesis**

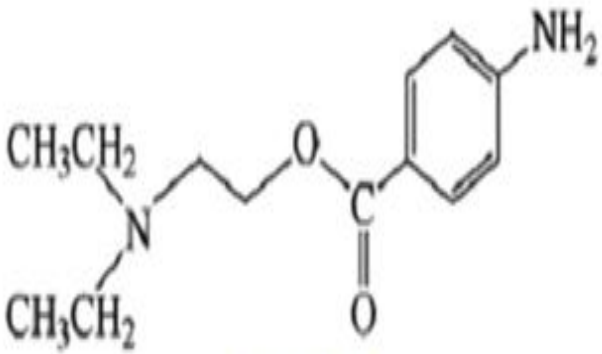


cocaine
lead compound

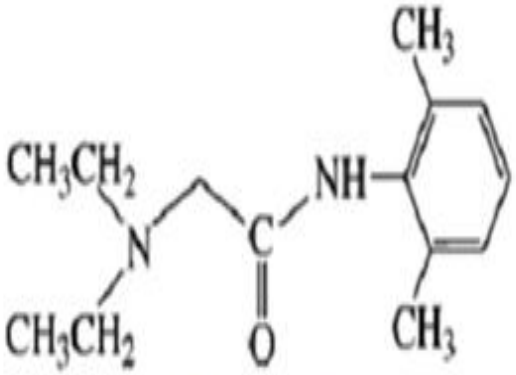
local anesthetic, but bad effect on the central nervous system



procainamide hydrochloride



procaine
Novocain



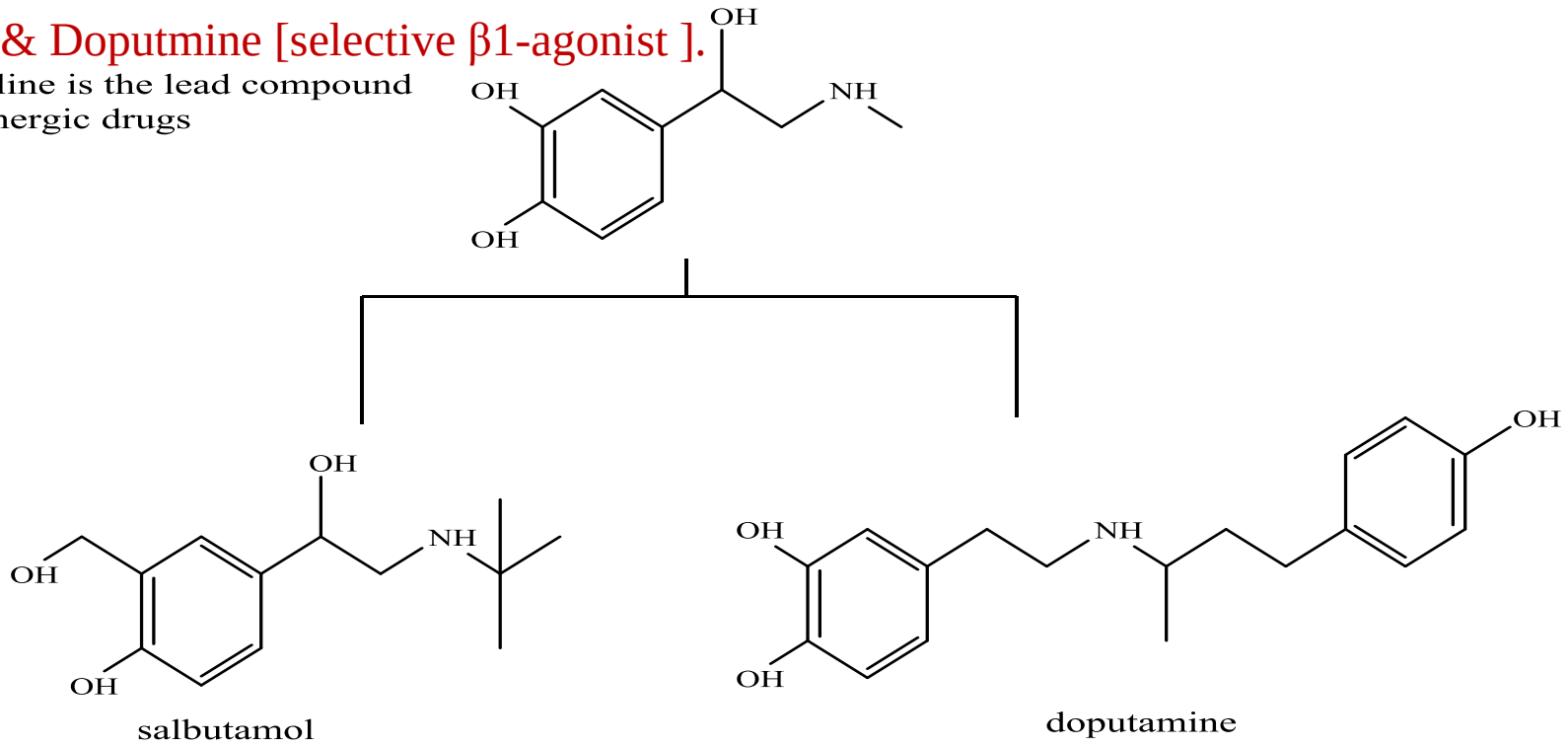
lidocaine
Xylocaine

Sources of leads compounds

2. Animal. Some modern drugs derived from animal sources because the synthesis of such chemicals is very cumbersome and expensive. Example; gonadotrophins, heparin, insulin, adrenaline (epinephrine) ,thyroid extracts and enzymes.

example Adrenaline' used in development of adrenergic β-agonist as Salbutamol [selective β2-agonist] & Doputmine [selective β1-agonist].

Adrenaline is the lead compound of adrenergic drugs



salbutamol

doputamine

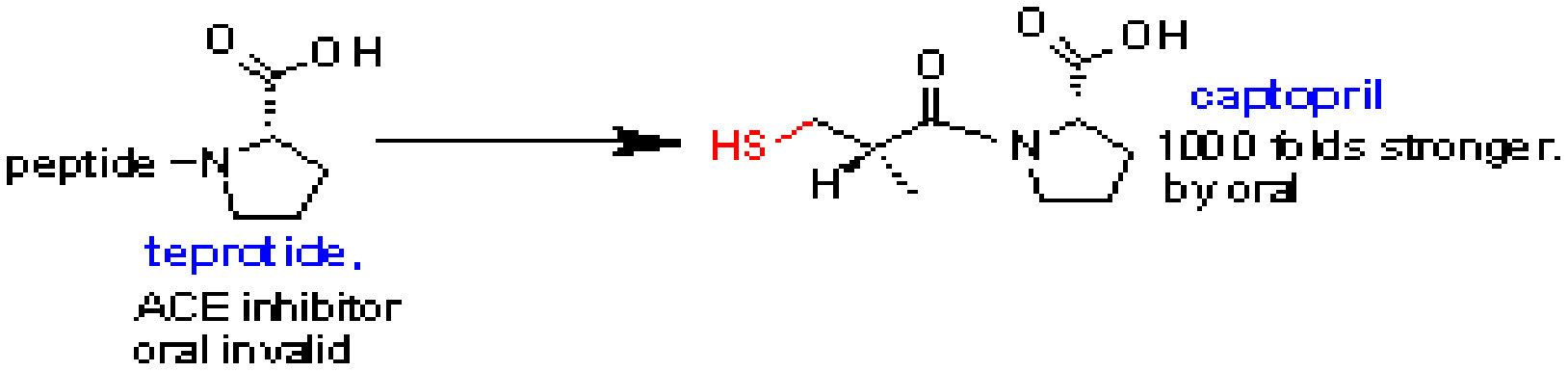
Sources of leads compounds

3. Venoms and toxins

Venoms and toxins have been used as lead compounds in the development of novel drug for example:

1- Teprotide a peptide isolated from the venom the Brazilian viper was a lead for the development of the Captopril antihypertensive agent.

2- Neurotoxins isolated from serious food poisoning(botulism) but have clinical use as well. They can be inject to specific muscle such as those controlling the eyelid to prevent a spasm by prevent cholinergic transmission (lead for development novel anticholinergics drugs).

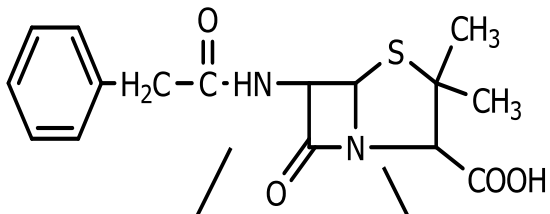


Sources of leads compounds

4. Microorganisms: a large number of antibiotics have been discovered from a variety of soil fungi and some bacteria. Example; Penicillin, Streptomycin, Tetracycline.

Penicillin G is the LEAD COMPOUND ?

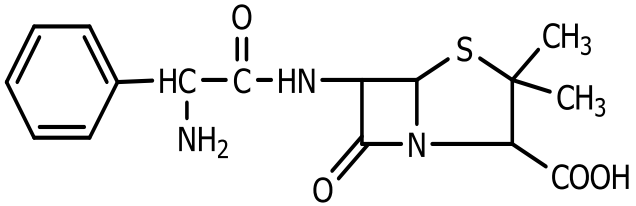
Isolated from P.notatum & P.chrysogenum



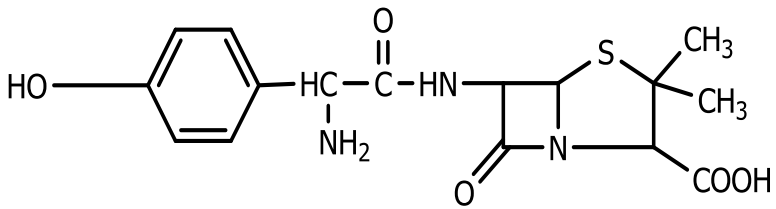
Problems [Limitation] of penicillin G:?

1- Narrow spectrum
2- Inactive orally [acid-labile] only injection.?
3- lactamase [penicillinase] sensitive to enzyme produced by resistant bacteria.?
4- Short duration of action

Modification of lead to improve the activity and absorption



Ampicillin



Amoxicillin

Sources of leads compounds

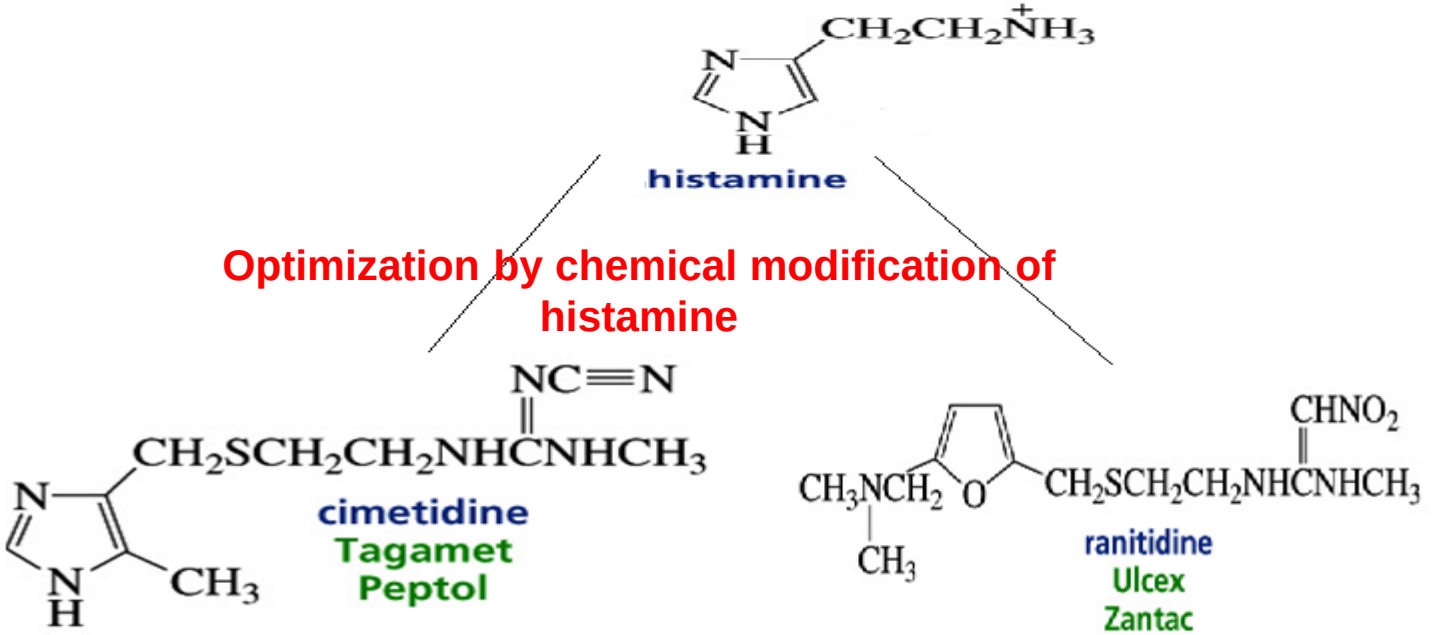
5- Natural ligands for receptors

Example;

1-Adrenaline, nor adrenaline and acetylcholine are used as the leads compounds for development of adrenergic drugs and cholinergic drugs.

2- Histamine was used as the lead compound for development of H1 and H2 histamine antagonist example cimetidine. Turning an agonist into antagonist is frequently achieved by adding extra binding groups to the lead structures.

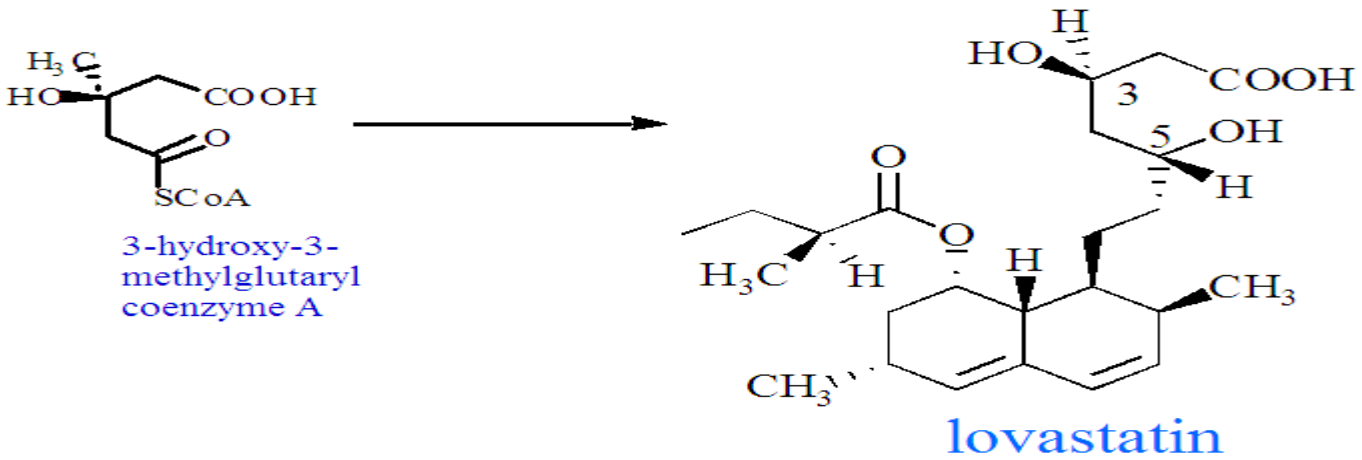
Excess histamine causes the symptoms associated with the common cold and allergic responses and gastric ulcer



6- Natural substrates for enzymes

Example 3-hydroxy-3-methylglutaryl coenzyme A substrate is a lead compound of Antihypercholesterolemic drugs.(HMG-CoA reductase inhibitors).

Rate-determining step in cholesterol biosynthesis is conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonic acid by HMG-CoA reductase



About one-quarter of FDA-approved drugs are enzyme inhibitors (HW).

Robertson, J. G. *Biochemistry* **2005**, *44*, 5561-5571.

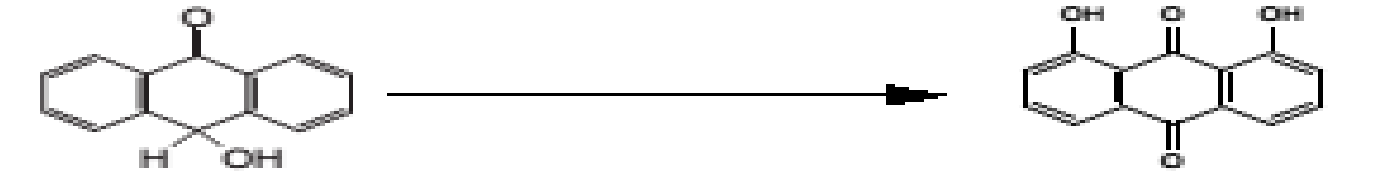
7- Enzymes products: fore example the design of the carboxypeptidase inhibitor L-benzylsuccinic acid arising from the carboxypeptidase-catalysed hydrolysis of peptides (examples: ACE inhibitors) (HW)

Sources of leads compounds

8- Medical folklore

Example; Anthraquinones [active constituent in rhubarb root]

is a lead compound in design of Danthron [laxative].



Anthraquinones Danthron

9-Searching synthetic compounds (bank)

Thousands of compounds synthesized by organic chemists are

stored in synthetic banks available for screening as medicinal leads.

E.g.1- Isoniazid [anti-T.B.drug]

Isoniazide is lead compound

Isoniazid pyrazinamide

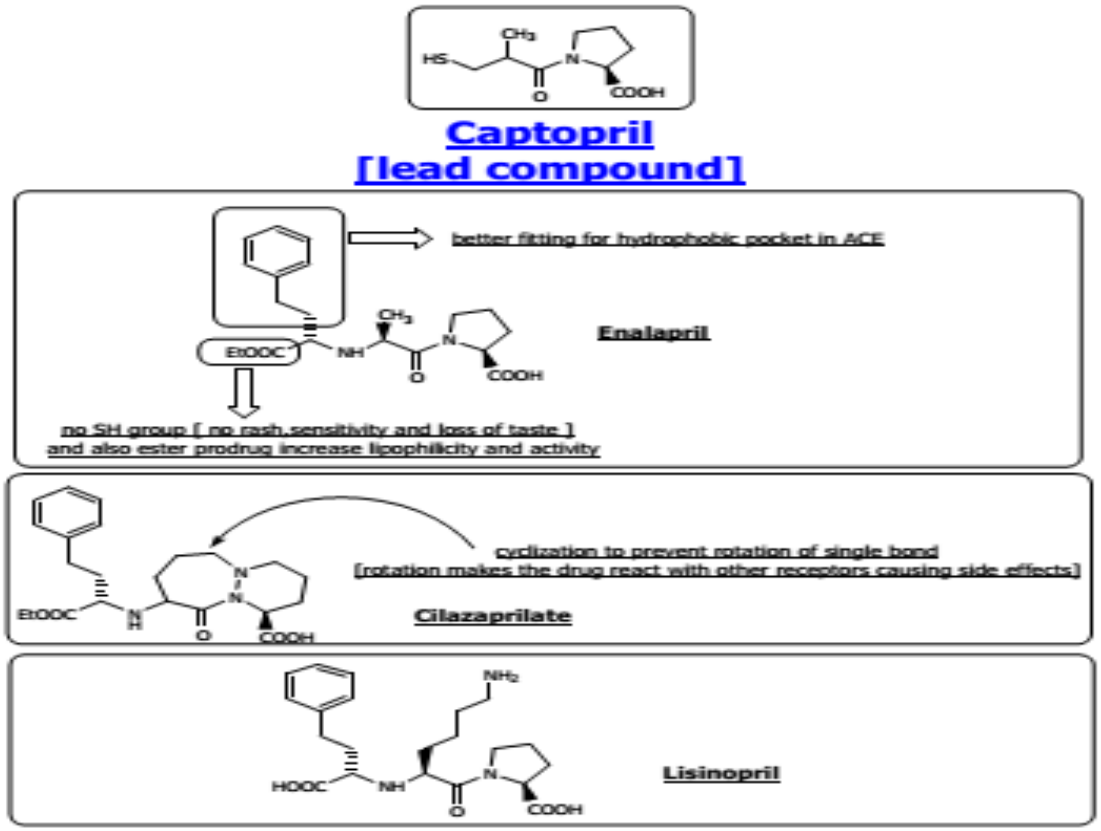
Sources of leads compounds

9- Existing drugs:

E.g. :Captopril [anti-hypertensive] was used as a lead for

Cilazaprilate, Lisinopril& Enalapril [more selective , potent, long acting & with lower side

effects].



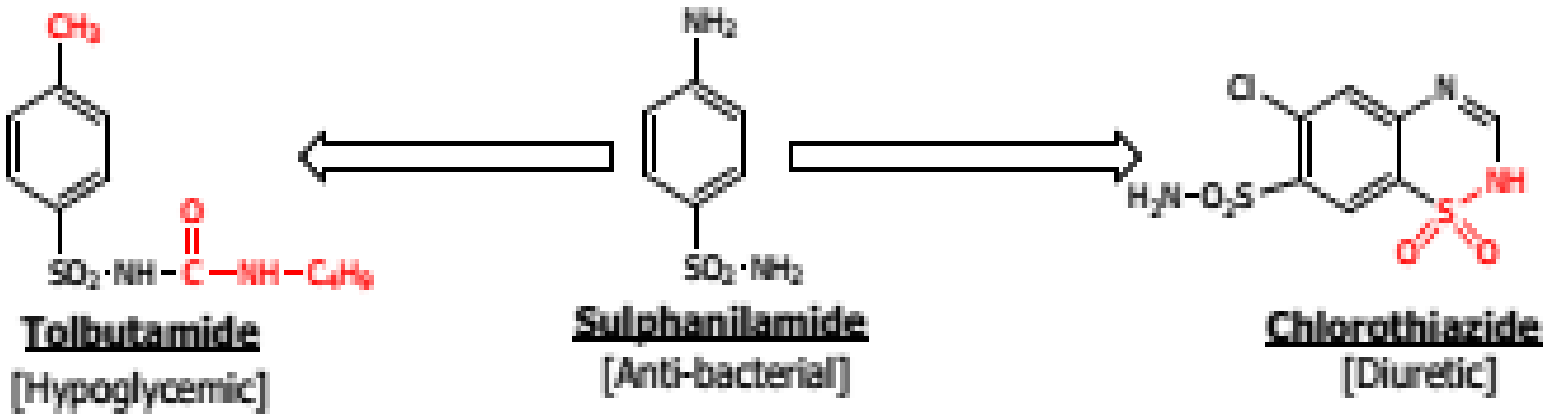
Sources of leads compounds

10- Enhancing aside effect:

E.g. : Sulphonamides [anti-bacterial],but with the following side effects

1) Hypoglycemia 2) Diuretic

Choosing a known drug as the lead compound for a side effects has the advantage that compound is already drug like and more feasible to develop pharmacokinetic and pharmacodynamics properties

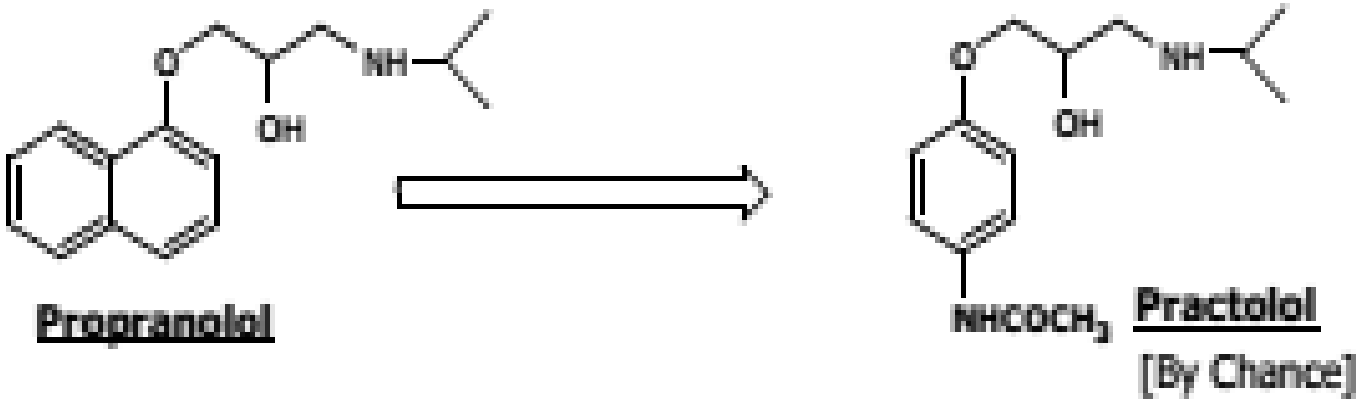


Sources of leads compounds

11- Serendipity [by chance] example :

[a]Nitrogen mustard used as anti-leukemia a. It was observed that persons who inhaled gas during second world war lost their natural defense against microbes due to WBCs destroyed

[b] Propranolol and its analogues [non-selective β-blocker & lipophilic with CNS side effects] during the decrease of CNS side effects 'by introduction of amide group "hydrophilic group" by chance' Practolol was found to be a selective β1-blocker & with less side effects]



[c] Promethazine was synthesizes as antihistamine for possible use in surgical shock and was found to make patients relaxed and unconcerned . This led to discovery of an antipsychotic drug. (HW).

Sources of leads compounds

12- Combinatorial and parallel synthesis:

Combinatorial chemistry involves creating a large number of molecules and quickly testing them for desirable biological activity. Example create a library of Benzodiazepines.

13- Computer- aided design of lead compounds

New lead compounds can be found by carrying out computerized researches of structural databases. Example docking experiments(program) can be carried out if the structure of target binding site is known.

Properties of leads compounds

- Some of lead compound that have been isolated from natural source have sufficient activity without serious side effect used directly in medicine for example morphine, quinine.
- Most lead compounds with low activity or unacceptable side effects, its necessary required to improvement by chemical modification.
- If the aim of research is to develop an orally active compounds, certain properties of the lead compound or Lipinski's rules should be taken into account which are:

1) molecular weight < 500
2) logP < 5
3) < 5 H-bond donors (sum of NH and OH)
4) < 10 H-bond acceptors (sum of N and O)
5) < 10 rotatable bonds An additional rule was proposed by **Veber**

Otherwise absorption and bioavailability are likely to be poor. NB This is for **oral drugs only.**

- When a compound is nearing nomination for entry to clinical trials, we need to look at: Solubility, and Chemical stability (Look at stability to pH, temperature, water, air, etc)

Isolation and purification of lead compound

- If the lead compound is present in a mixture of other compounds, obtained from a natural sources or from a combinatorial synthesis, it has to be isolated and purified..
- Isolation and purification methods depends very much on the structure, stability, and quantity of the compound.
- Type of techniques available to help in the isolation and purification of a natural product .

1. **Filtration:** Only one of the compounds is soluble in the given solvent.
2. **Crystallization:** Impurities and organic compound have different solubilities in the given solvent.
3. **Sublimation:** Used to separate volatile organic compounds from non volatile impurities.
4. **Distillation** difference in boiling points of compounds.
5. **Differential extraction** Used to extract pure organic compounds from their aqueous solution by shaking with organic solvent in which they are highly soluble.
6. **Chromatography techniques** Used to purify small samples. Based on selective adsorption or partition between stationary and mobile phase. Example TLC, CC, HPLC and GC.

Structural determination of lead compound

- The micro analysis of cholesterol was carried out in1888 to get its molecular formula, but its chemical structure was not fully established until an X ray crystallographic study was carried out in1932.

- Types of technics used for structural determination:

1) NMR,H1and C13.
2) Mass spectroscopy
3) IR spectroscopy determine the type of functional groups.
4) X-ray crystallographic confirmed structure .

- Important of structural determination of lead:

1. Optimize and improve of lead structure
2. Study the physico– chemical properties of lead
3. Study of pharmaceutical, pharmacokinetic and pharmacodynamics.
4. Design the method of synthesis.
5. Synthesis of analogues.

Drug design optimization process

- **The 'drug design**

Creation of newer drug molecules based on biologically-active-prototypes (lead) derived from either plant or animal kingdom, synthesis of congeners displaying interesting biological actions, the basic concept of isosterism and bioisosterism, and finally precise design of a drug to enable it to interact with a receptor site efficaciously.

- **Objective of drug design:**

1. Increase activity.
2. Increase selectivity for target.
3. Decrease side effects.
4. It should be easily synthesized and be chemically stable.
5. It should have acceptable pharmacokinetic properties and be non toxic.

Pharmacodynamics and Pharmacokinetic properties should have equal priorities in influencing which strategies are used and which analogues are synthesized.

Drug design optimization process

A. Identify structure-activity relationships(SARs).

- Once the structure of a lead compound is known, it necessary to study its SAR for discover which parts of the molecule (functional groups) are important to biological activity and which are not.

- **Determination of SARs ?**

1. If the lead target interaction crystalized, the crystal structure of the complex could be solved by X-ray crystallography method and identify ctionalthe important binding interaction.
2. If the lead target cannot be crystalized, the SAR can be determined by preparing a selected number of compounds, which vary slightly from the original molecule where the functional group is modified or removed in order to see whether activity is affected by such achange.

- For example :Modification of Glipine .

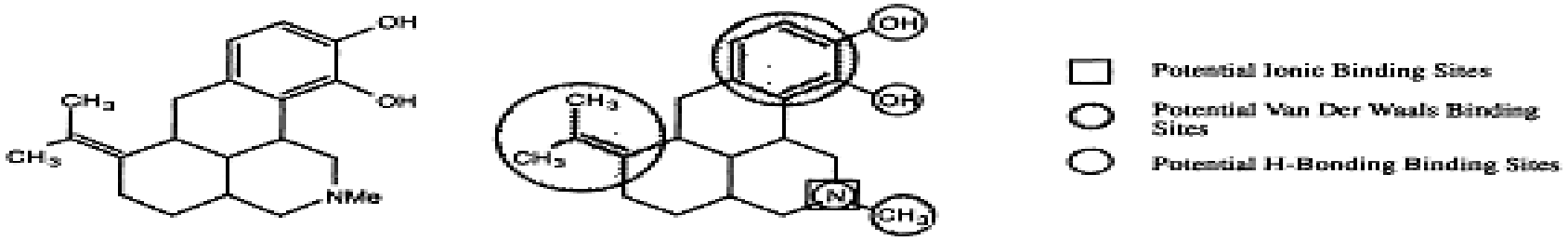


Fig. 7.3 Glipine.

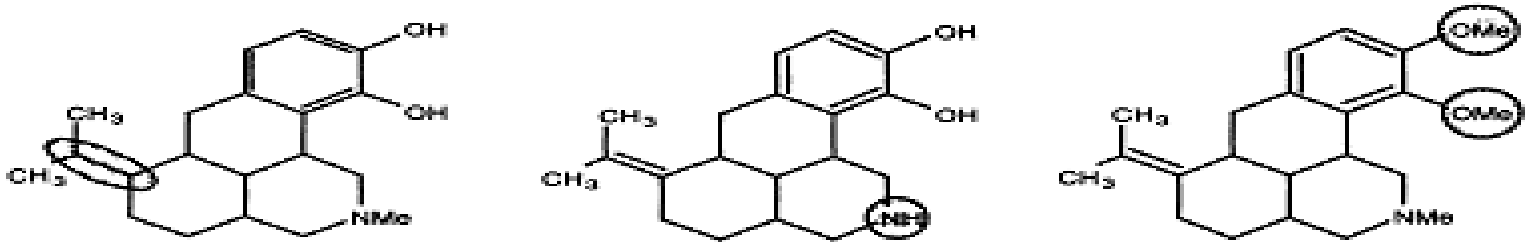


Fig. 7.4 Modifications of glipine.

Drug design optimization process

A. Identify structure-activity relationships(SARs).

- The binding interactions that are possible for different functional groups and the analogues that could be synthesized to establish whether they are not involved in binding or not.

1) The binding role of hydroxyl groups

- Hydroxyl groups are commonly involved in hydrogen bonding . Converting such a group to a methyl ether or an ester is easy and will usually destroy or weaken such a bond.

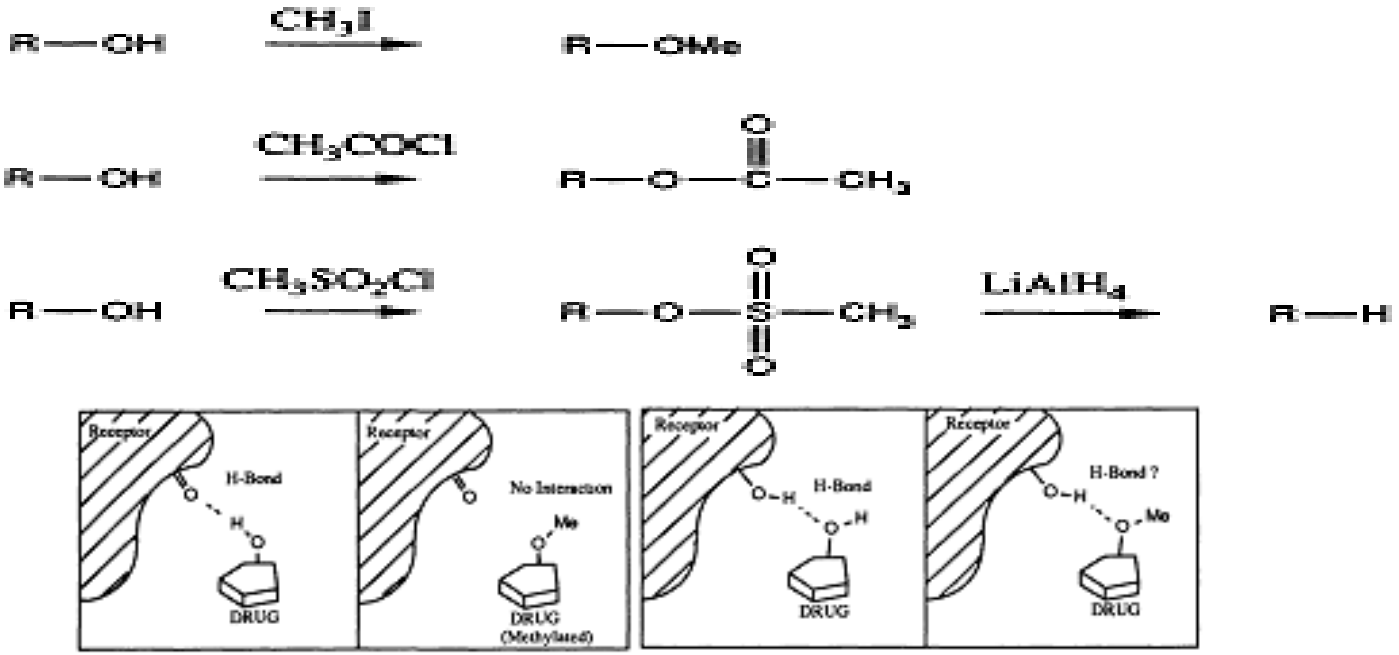


Fig. 7.6 Possible hydrogen bond interactions.

Drug design optimization process

A. Identify structure-activity relationships(SARs).

2, The binding role of amino groups

Amines may be involved in hydrogen bond in or ionic bonding ,but the latter is more common. The same strategy used for hydroxyl groups works here too . Converting the amine to an amide will prevent the nitrogen's lone pair taking part in hydrogen bonding or taking up a proton to form anion.

Tertiary amines have to be dealkylated first, before the amide can be made. Dealkylation is normally carried out with cyanogen bromide or achloroformate such as vinyloxycarbonylchloride

Fig. 7.8 Dealkylation of tertiary amines.

3. The binding role of aromatic ring

Aromatic rings are commonly involved in vander Waals interactions with f at hydrophobic regions of the binding site . If the ring is hydrogenated to a cyclohexane ring, The structure is no longer flat and interacts far less efficiently with the binding site

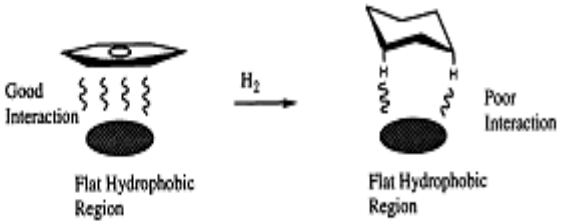


Fig. 7.9 Reduction in the binding efficiency of aromatic rings by hydrogenation.

Drug design optimization process

A. Identify structure-activity relationships(SARs).

4. The binding role of double bonds

Unlike aromatic rings , double bonds are easy to reduce and this has a significant effect

On the shape of that part of the molecule. The planar double bond is converted into a bulky alkyl group.

If the original alkene was involved in vander Waals bonding with a flat surface on the receptor ,reduction should weaken that interaction, since the bulkier product is less able to approach the receptor surface.

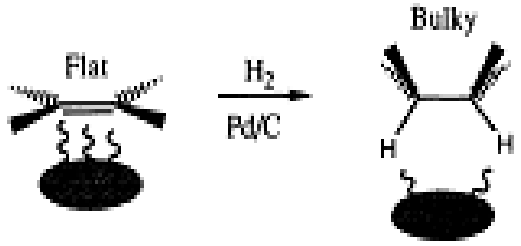


Fig. 7.10 The binding role of double bonds.

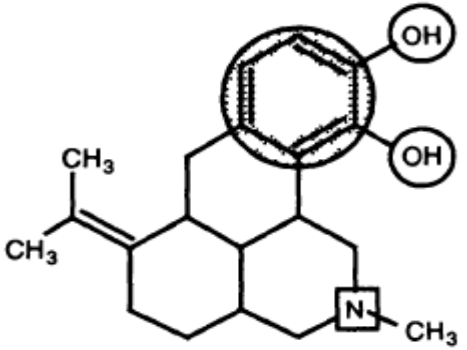
Note

- Functional groups such as alcohols, amines, ester, amides, caboxylic acids phenols and ketones can interacts with binding sites by means of hydrogen bonding.
- Functional groups such as amines, quaternary ammonium salts and caboxylic acids can interacts with binding sites by means of ionic bonding.
- Functional groups such as alkenes and aromatic rings can interacts with binding sites by means of vander Waals and hydrophobic interaction.
- Reactive functional groups such as alkyle halides may lead to irreversible covalent bond between a lead compound and its target.

Drug design optimization process

B. Identification of a pharmacophore

- The pharmacophore summarizes the important binding groups which are required for activity, and their relative positions in space with respect to each other. Example the pharmacore for glipine are the two phenol groups, the aromatic ring and the nitrogen atom.



GLIPINE

C. Lead or drug optimization

- Once the pharmacophore of the lead compound have been identified, it is possible to synthesize analogues that contain the same pharmacophore. But why is this necessary? If the lead has useful biological activity, why bother making analogues? The answer are the cardinal objective of drug design
- The **cardinal objectives** of the **method of variation** are :

- To improve potency
- To modify specificity of action
- To improve duration of action
- To reduce toxicity
- To effect ease of application or administration or handling
- To improve stability and to reduce cost of production

Drug design optimization process

C. Lead or drug optimization mthodes

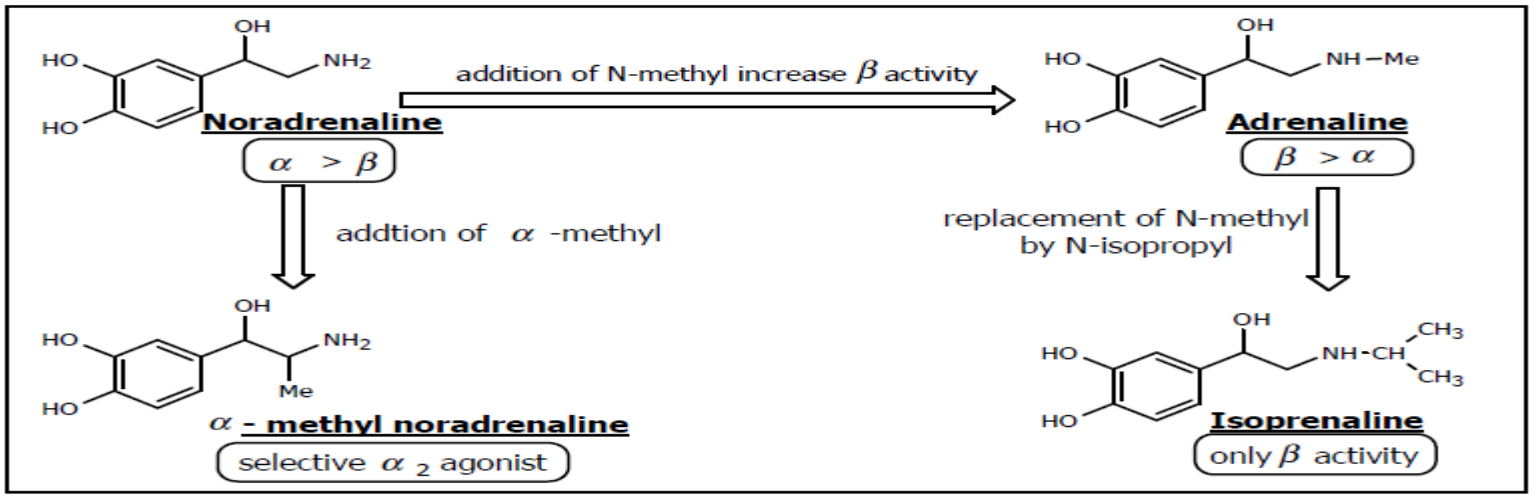
Various strategies have been used for better drug-target interaction :

1. Variation of substituents. 2. Extension of structure.3. Chain extension / contraction.4.Ring extension / contraction. 5.Ring variation. 6.Ring fusion. 7. Isosterism. 8. Simplification of the structure. 9.Rigidification of the structure.

1) Variation of substituents

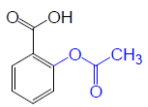
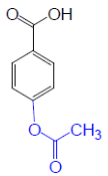
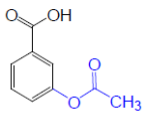
a. Alkyl substituents

- The length and size of alkyl substituents can be modified to fill up hydrophobic pocket in the binding site or introduce selectivity for one target over another . **N-alkyl substituents :** has important role in selectivity of some drugs, for E.g. :



b. Aromatic substituents :

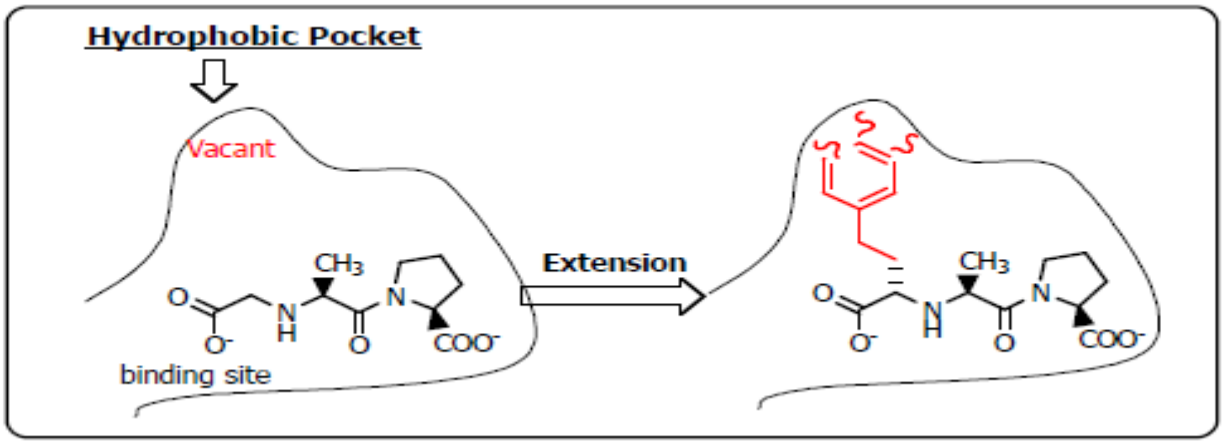
Positional change of aromatic substituents :

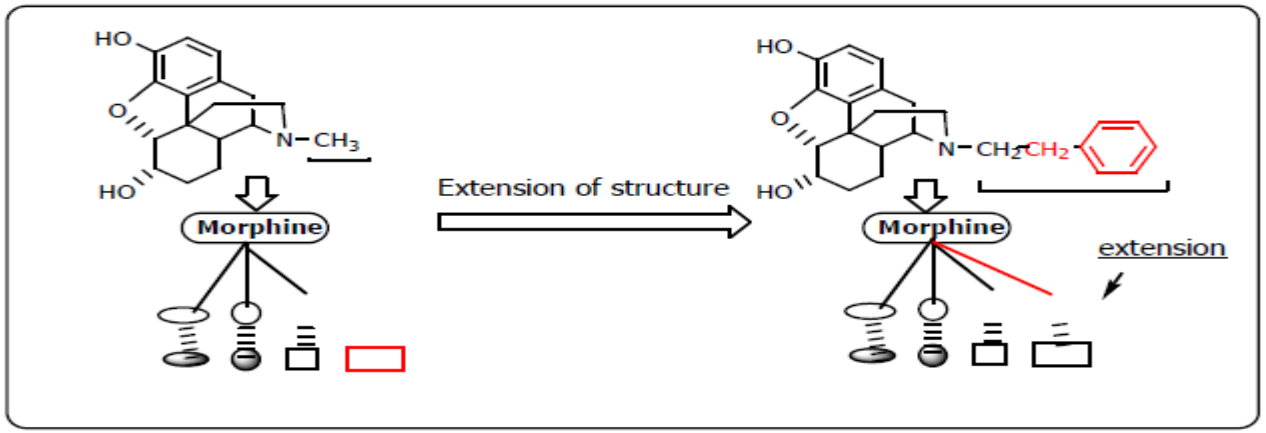
Drug design optimization process

2. Extension of the structure (extra functional groups are added to lead compound in order to interact with extra binding regions in the binding site)

- E.g.1 : phenyl ethyl group . 1000 fold improved activity



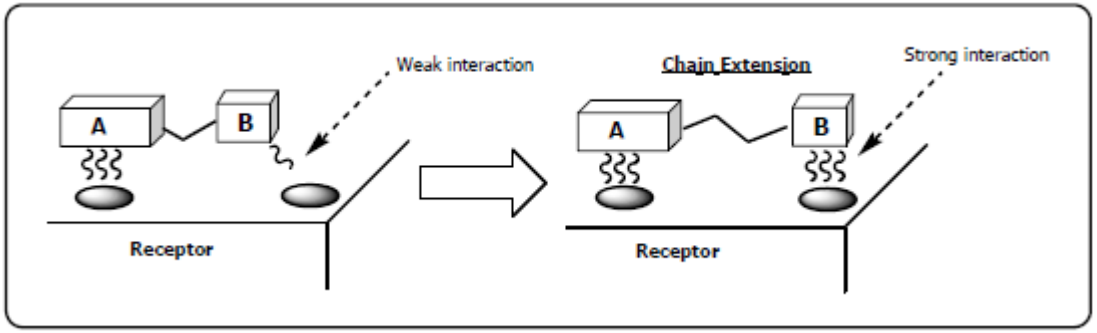
E.g.2 :Morphine
addition of Phenyl ethyl group to morphine . Phenyl ethyl morphine [which is 14 times more active] ,



Drug design optimization process

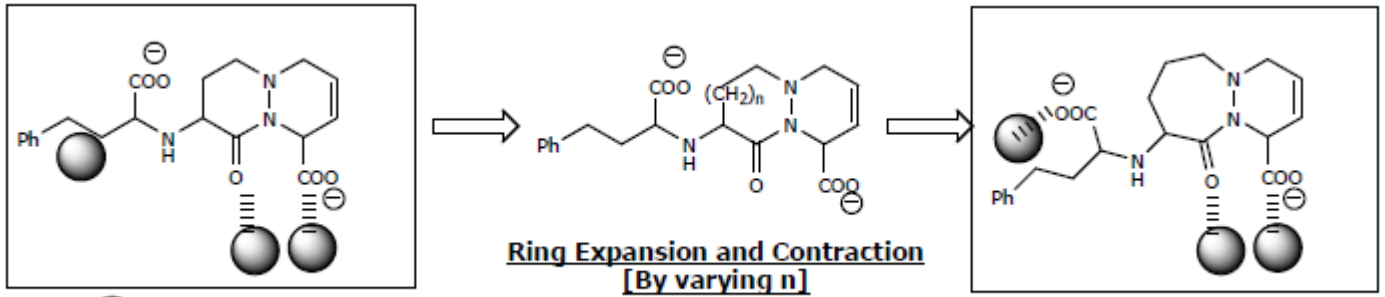
3. Chain Extension / Contraction

For drugs having two important binding groups separated by a chain of specific length. The chain can be modified in length in order maximize the interactions of each group with corresponding binding region



4. Ring Expansion / Contraction

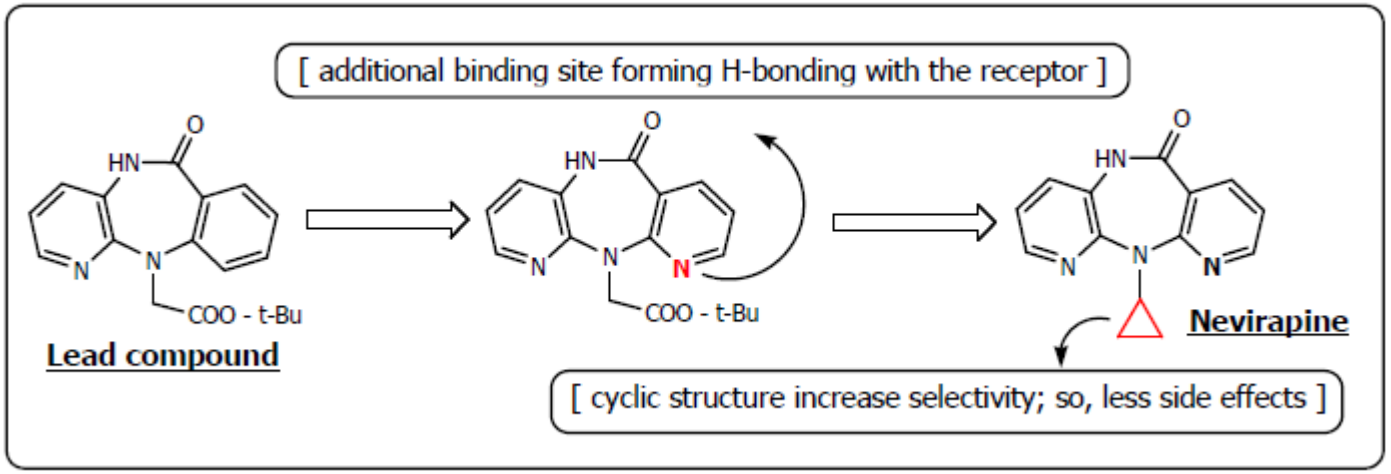
Ring linking important binding group can be expanded or contracted such that the binding groups bind efficiently with relevant binding regions.
E.g. development of Cilazaprilate [ACE inhibitor].



Drug design optimization process

5. Ring Variation

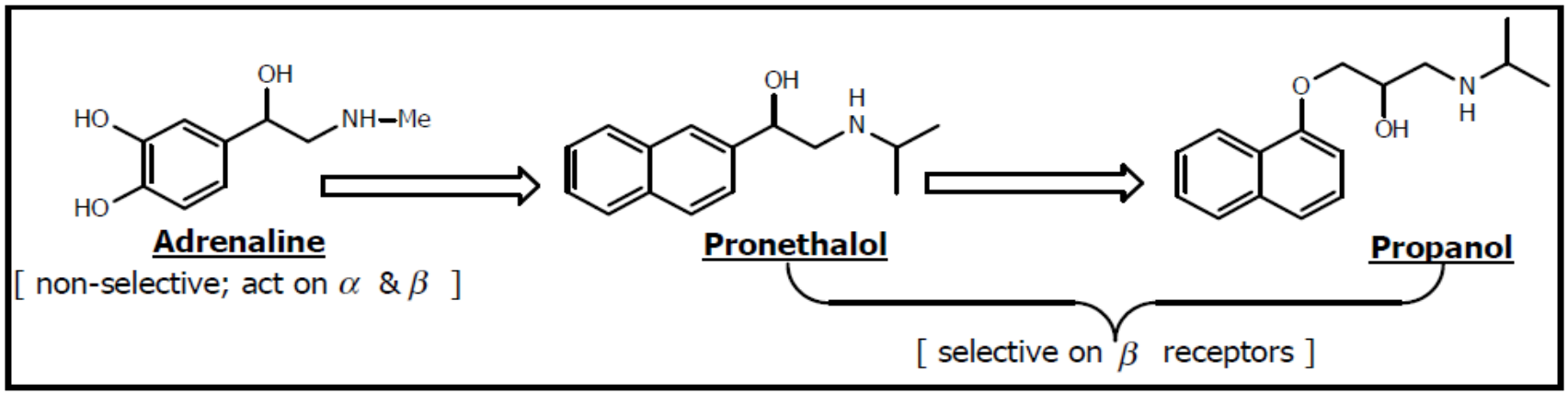
E.g. Nevirapine [anti-viral]



6. Ring Fusion

Ring fusion may .. interaction or selectivity.

E.g. Pronethalol [selective β-blocker],



Drug design optimization process

7. **Simplification of the structure**

E.g. Simplification of Cocaine . many local anesthetics as Procaine

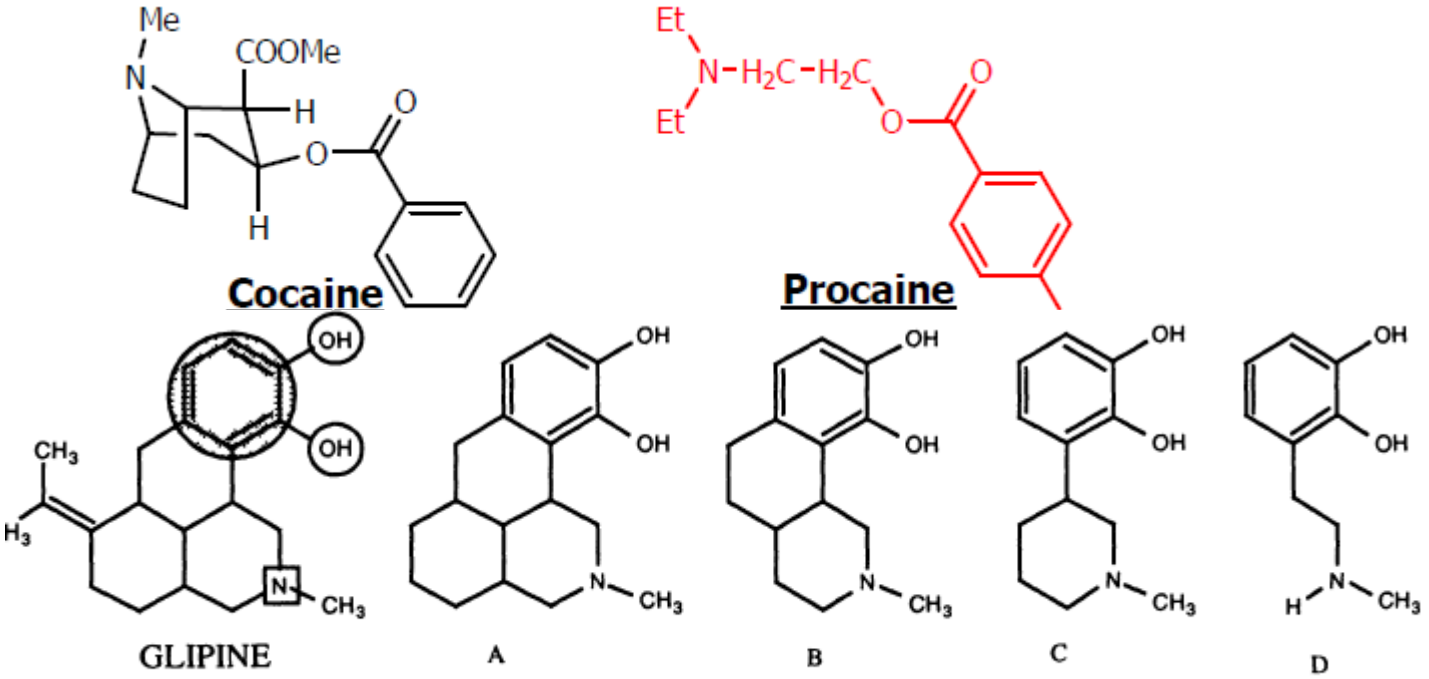


Fig. 7.20 Glipine analogues.

Steps of simplification of the structure :

1. Identify; the essential groups
2. Discard ; non-essential parts of the structure without losing activity

Advantages :easier , quicker and cheaper to synthesize in the laboratory.

Drug design optimization process

8. Rigidification of the structure

Rigidification increase activity & decrease side effects.

Methods of Drug Rigidification (Methods of Conformational Restriction) :

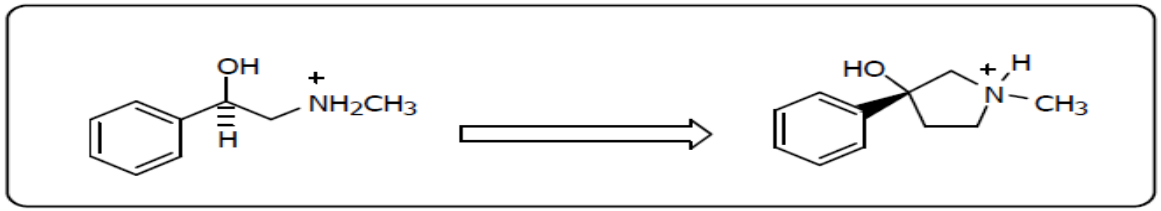
1.Unsaturation : by introduction of a double or triple bonds.

2. Cyclization.

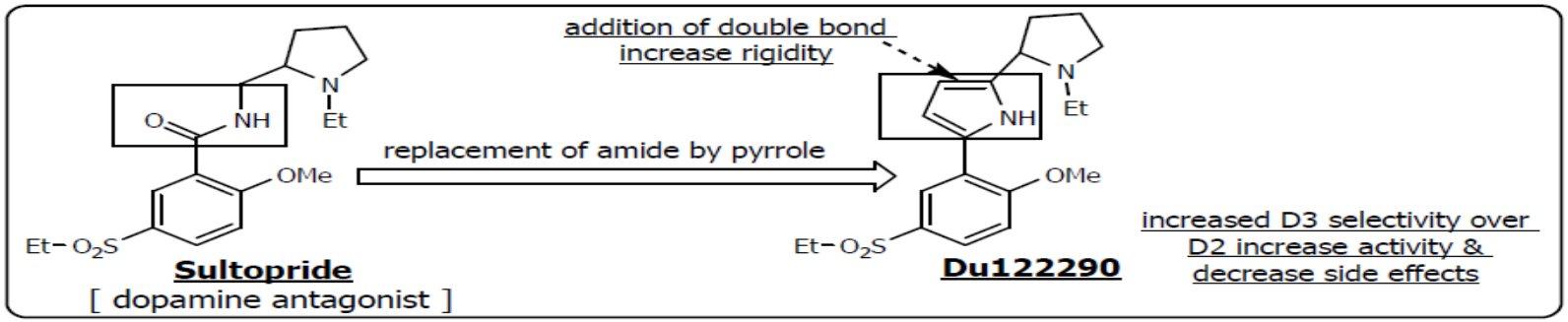
3. Steric hindrance : by methyl groups

4. Addition of groups forming intramolecular hydrogen bond.

E.g. 1 :



E.g. 2 :



Drug design optimization process

9. Isosteres and Bioisosters

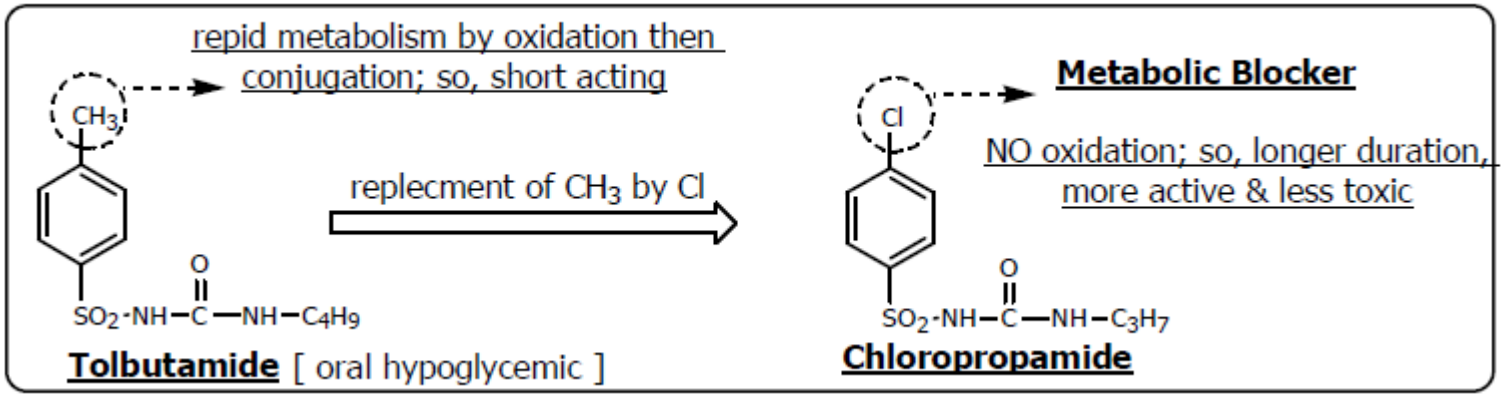
- Isosteres have often been used in drug design to vary the character of the molecule in rational with respect to features such as size, polarity, electronic distribution and bonding.
- **Isosteres** are atoms or groups of atoms which have the same valency (or number of outer shell electrons). For example, SH, NH2, and CH3 are isosteres of OH, while S, NH, and CH2 are isosteres of O. Isosteres have often been used to design an inhibitor or to increase metabolic stability.
- Bioisostere is a chemical group which can replace another chemical group without affecting biological activity.

[i] Classical Bioisosteres

Must have the same shape, size & outer electronic configuration

. it's subdivided into :

a. Monovalent atoms or groups (-CH3 , -NH2 , -OH , -Cl , -F) :



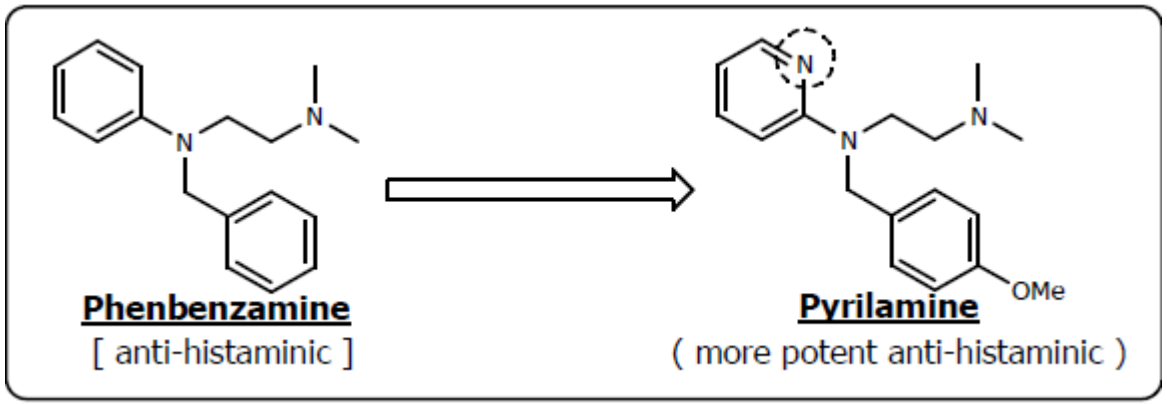
Drug design optimization process

9. Isosteres and Bioisosters

[i] Classical Bioisosteres

b. Divalent atoms or groups (-CH2, -NH , -O- , -S-) :

c. Ring equivalents :



Drug design optimization process

9. Isosteres and Bioisosters

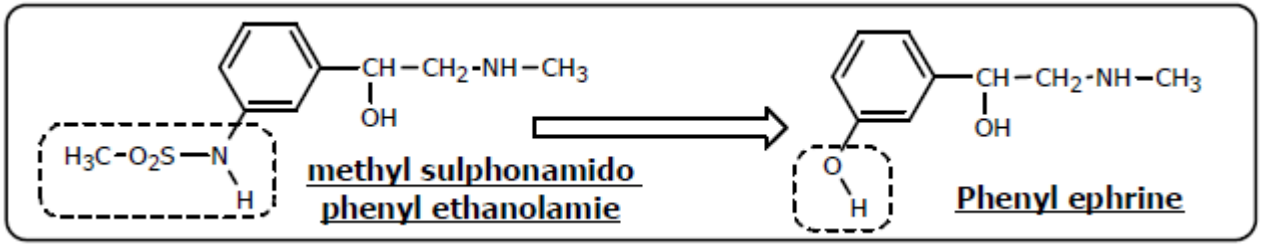
[ii] Non Classical Bioisosteres

Non isosteric groups are used as bioisosteres regardless their steric or electronic effects
They retain biological activity by sharing a common key parameter :

1. Partition coefficient.
2. Electrostatic potential.

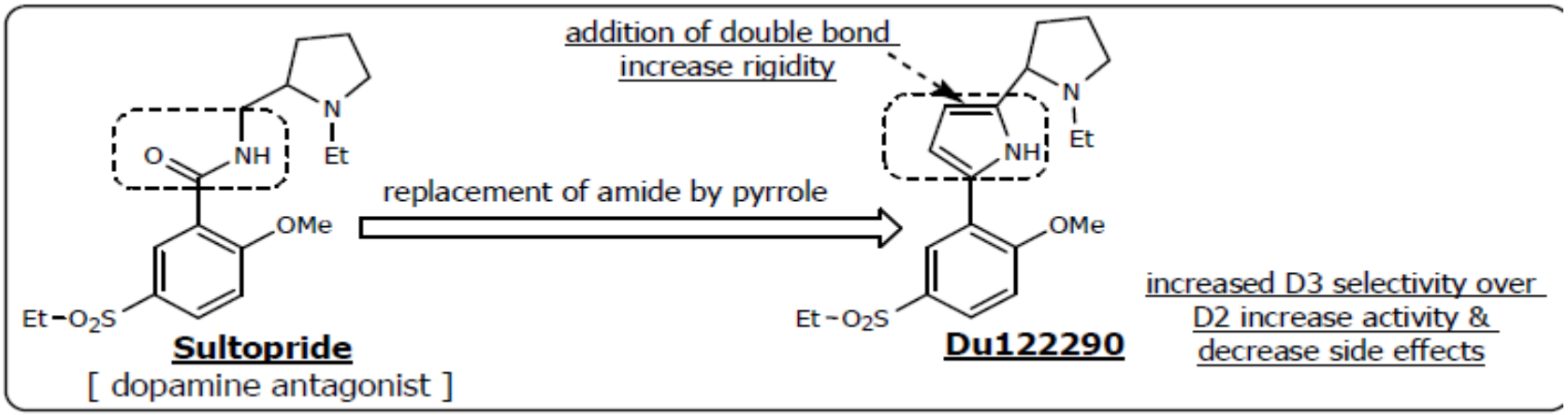
Subdivided into :

1. Exchangeable groups



2. Ring vs non-cyclic derivatives :

Amide function may be replaced by a pyrrole ring. E.g.**:**

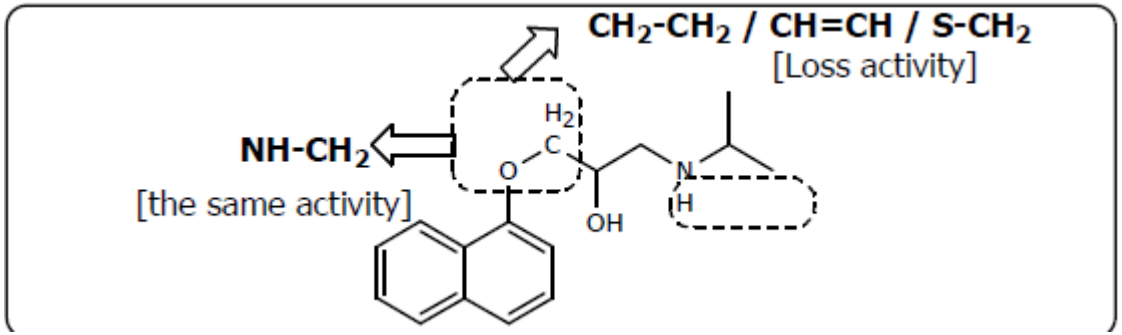


Drug design optimization process

Uses of Isosteres

1. to determine whether a particular group is involved in H-bonding :

- **E.g**. Propranolol

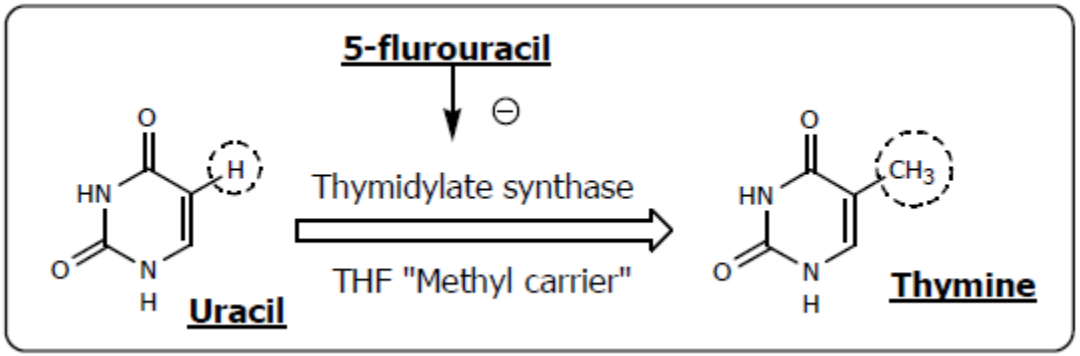


2. to determine the importance of size or electronic configurations towards activity :

F is an isostere to H and has the same size but it is more electronegative

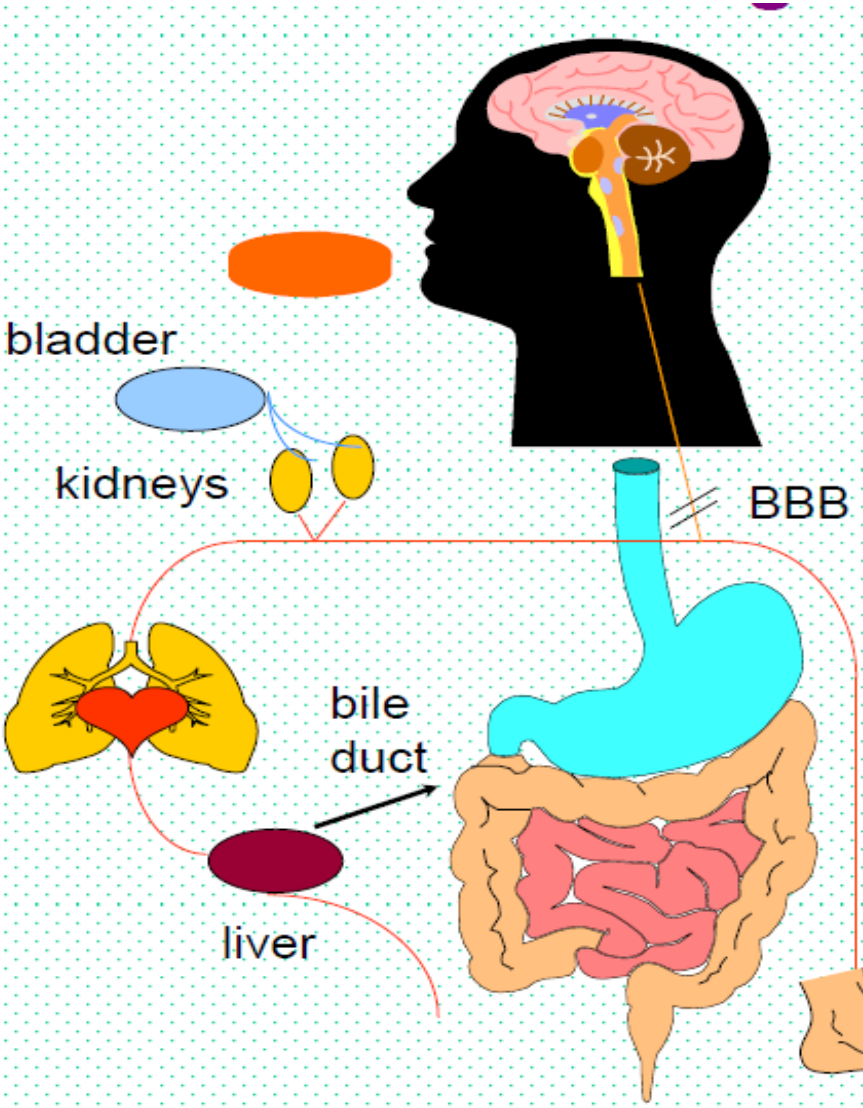
E.g

5-flurouracil [anti-cancer] competes with uracil [normal substrate] at target enzyme. F-C bond is not easily broken



Drug design optimization process

D- Improve pharmacokinetic properties



An "ideal" oral drug must be able to:

- dissolve
- survive a range of pHs (1.5 to 8.0)
- survive intestinal bacteria
- cross membranes
- survive liver metabolism
- avoid active transport to bile
- avoid excretion by kidneys
- partition into target organ
- avoid partition into undesired places (e.g. brain)

Drug design optimization process

D. Improve pharmacokinetic properties

The success of the journey depends principally on the physical properties of the drug. First of all, it has to be **chemically stable** and not break down in the acid conditions of the stomach. Secondly, it has to be **metabolically stable** so that it survives the hydrolytic enzymes present in the digestive system, liver, and blood stream. Thirdly, it has to have the correct **balance of hydrophilic to hydrophobic**.

❑ *Drug design for pharmacokinetic problems*

Drug design aimed at solving any or all of the above problems can involve a lot of trial and error, basically because of the many variables involved. However, there are some strategies which can be usefully employed.

1. Variation of substituents

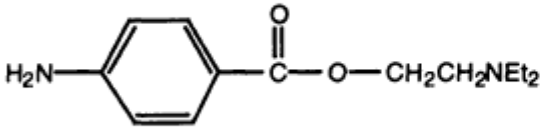
Easily accessible substituents can often be varied to improve the pKa and lipophilic properties of a compound. Such studies are particularly open to a quantitative approach known as the quantitative structure-activity relationship (QSAR) approach.

Drug design optimization process

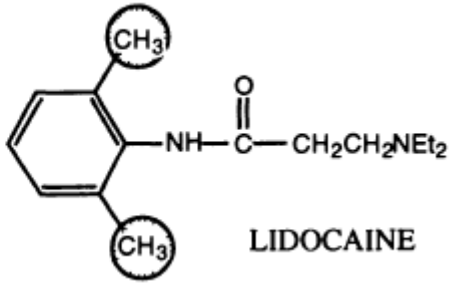
- ***Drug design for pharmacokinetic problems***

2. Stereoelectronic modifications

Procaine is a good local anesthetic, but it is short lasting due to the hydrolysis of the ester group. By changing the ester group to the less reactive amide group, chemical hydrolysis is reduced. Furthermore, the presence of two 0-methyl groups on the aromatic ring help to shield the carbonyl group from attack by enzymes.



PROCAINE



LIDOCAINE

A further example of these tactics is provided in the penicillin field with methicillin

Drug design optimization process

- ***Drug design for pharmacokinetic problems***

3. Metabolic blockers

- Some drugs are metabolized at particular positions in their skeleton. For example, the oral contraceptive megestrol acetate is oxidized at position 6 to give a hydroxyl group at that position.
- The introduction of a polar group such as this usually allows the formation of polar conjugates which can be quickly eliminated from the system.
- The introduction of a stable group such as a methyl group at position 6 can block metabolism and so prolong the activity of the drug.

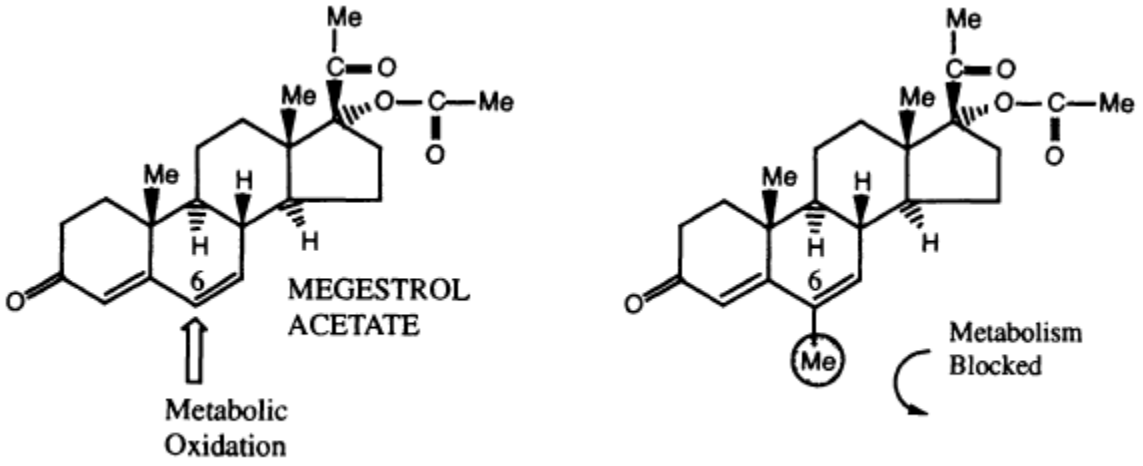


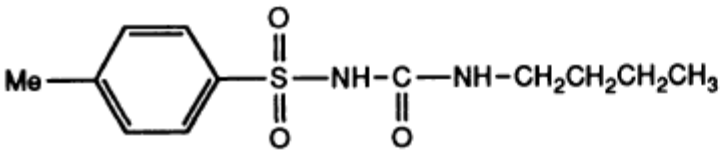
Fig. 8.6 Metabolic blockers.

Drug design optimization process

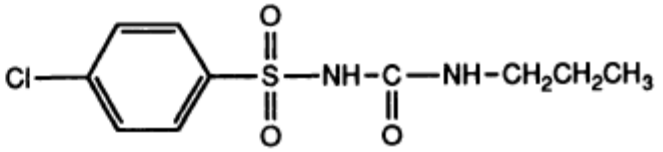
- ***Drug design for pharmacokinetic problems***

4 .Removal of susceptible metabolic groups

Susceptible groups can sometimes be replaced with groups that are stable to oxidation in order to prolong the lifetime of the drug. For example, the methyl group of the antidiabetic tolbutamide was replaced with a chlorine atom to give chlorpropamide which is much longer lasting

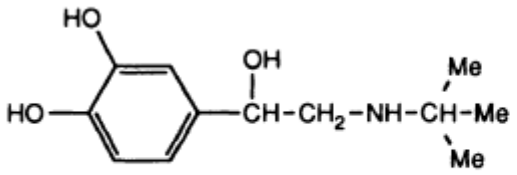


TOLBUTAMIDE



CHLORPROPAMIDE

Other example replace of hydroxyl group in salbutamol with hydroxymethyl group increase the duration of action due to inhibition of COMT,



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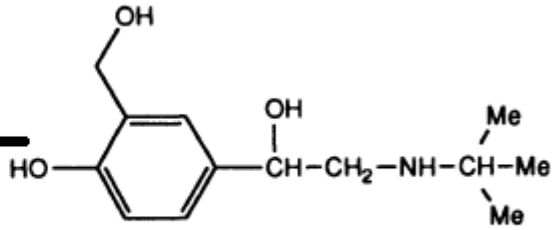

SALBUTAMOL

5. Prodrugs are compounds which may be inactive in themselves, but which can be converted by chemical or enzymatic means to an active drug. They have been useful in tackling problems such as acid sensitivity, poor membrane permeability, drug toxicity, and short duration of action.