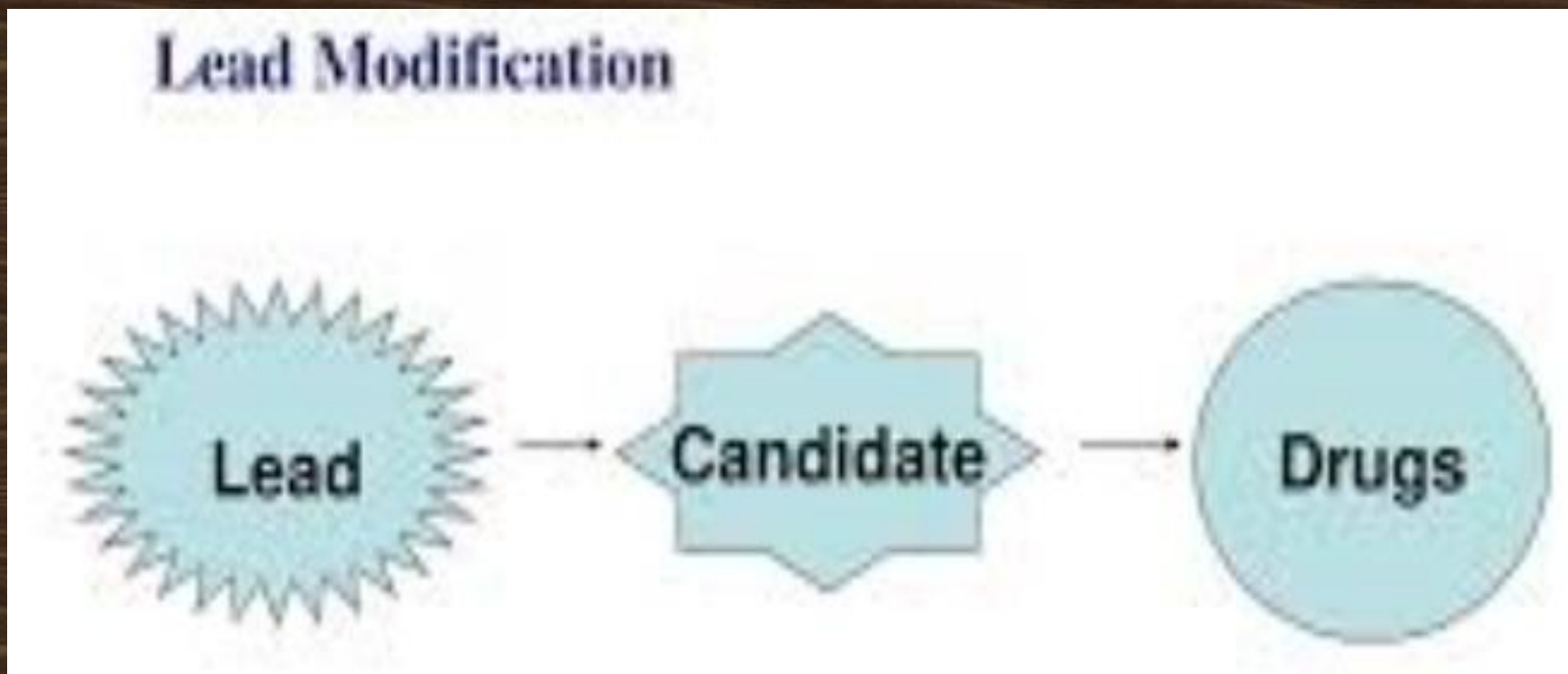# LEAD MODIFICATION

Course: **Drug Design**
Course code: **0510412**

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Learning Outcomes

At the end of this lesson students will be able to

➢ Define the lead modification and the lead molecule optimization.

➢ Describe the role of pharmacophore in lead molecule optimization.

➢ Explain about the structure-activity relationships (SAR).

➢ Describe the concept of bioisosterism in lead optimization and drug design.

➢ Explain the significance of physico-chemical properties such as lipophilicity and ionization of drugs in lead optimization.

Lead Modification

Lead modification is done to improve the Pharmacological activity.

1. **Identification of the active part: PHARMACOPHORE**

2. **Functional group modification**

3. **Structure-Activity Relationship (SAR)**

4. **Structure modification to increase potency and therapeutic index**

5. **Structure modification to increase oral bioavailability**

   - **Lipophilicity.**

   - **Effect of ionization.**

Lead Modification

1. **Identification of the active part: PHARMACOPHORE**

Pharmacophore- The relevant groups on a molecule that
interact with a receptor and are responsible
for the activity.

Auxophore- Other atoms in the lead molecule, may be
extraneous which may be interfering with the
binding of pharmacophore.

Lead Modification

Many roles of auxophore

❖ **Hold the pharmacophoric groups in their place.**

❖ **Interfere with the binding to the receptor…un-favorable.**

❖ **Occupy an inert space.**

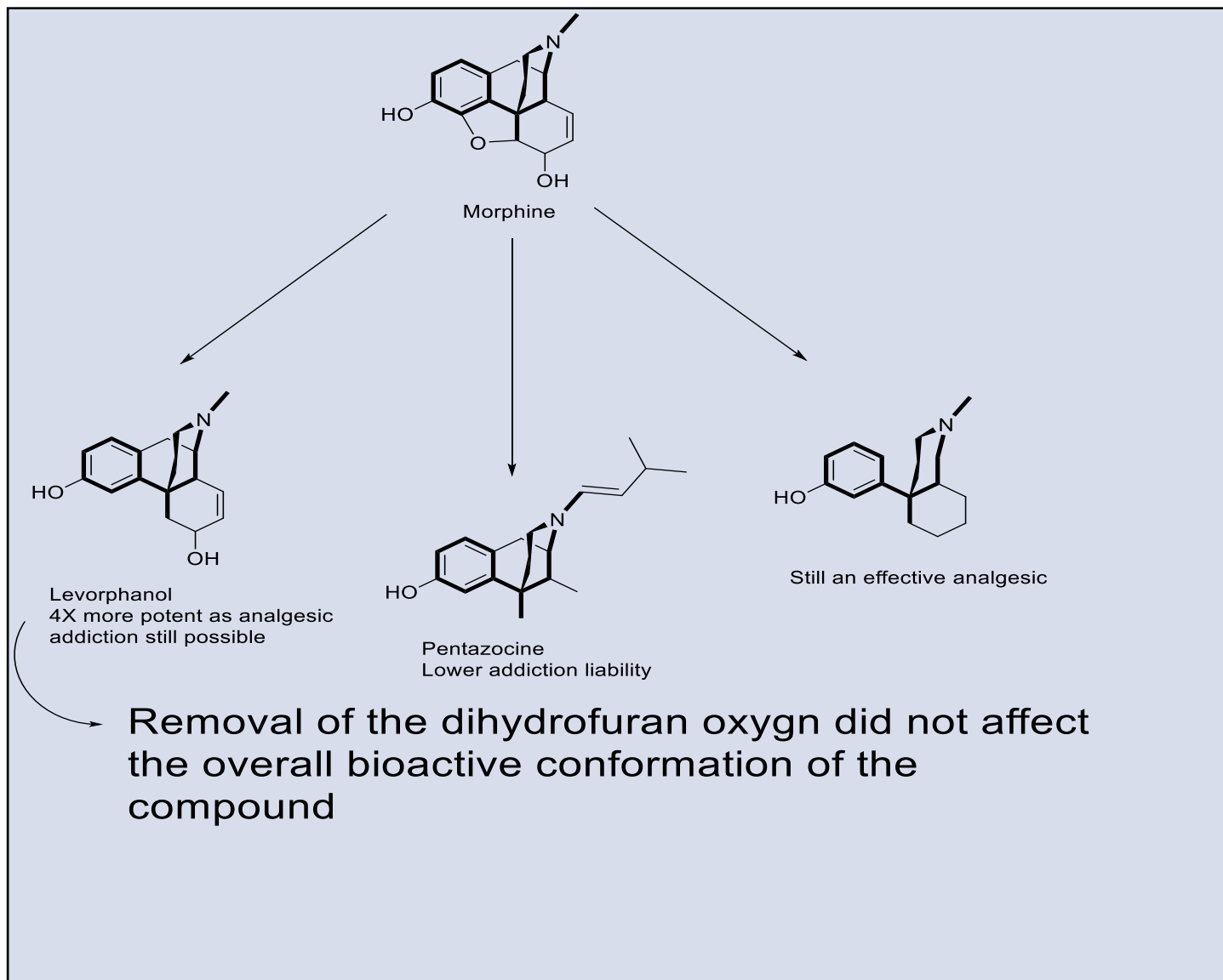❖ **Affect the pharmacokinetic properties of the whole structure.**
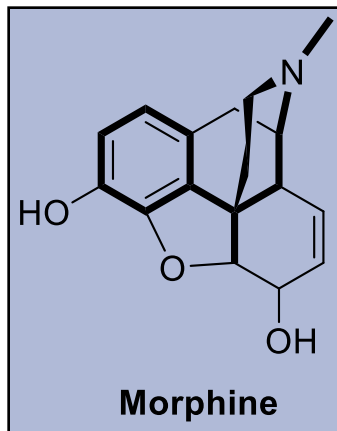
Opioid Analgesic (morphine)

Morphine

Bold style - pharmacophoric groups

Non-bold style - auxophoric groups

Lead Modification

Morphine

Levorphanol
4X more potent as analgesic
addiction still possible

Pentazocine
Lower addiction liability

Still an effective analgesic

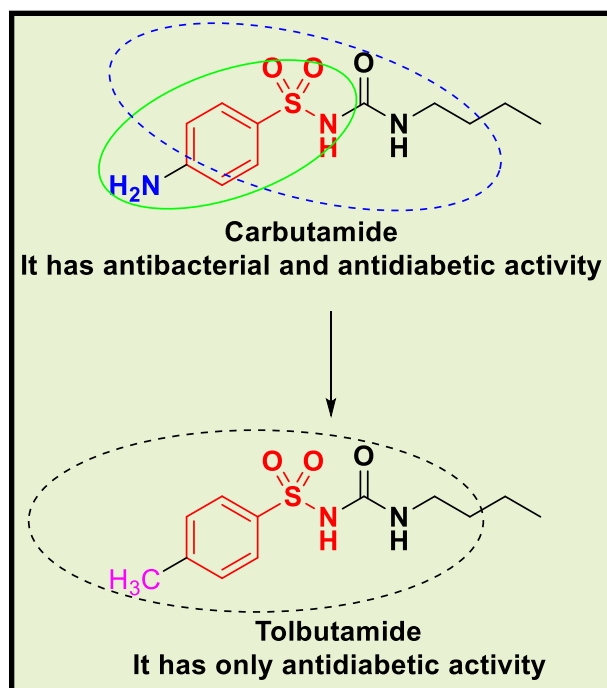Removal of the dihydrofuran oxygn did not affect the overall bioactive conformation of the compound
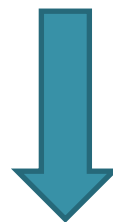
Lead Modification

2. Functional group modification

Replacement of the functional group yields beneficiary effect

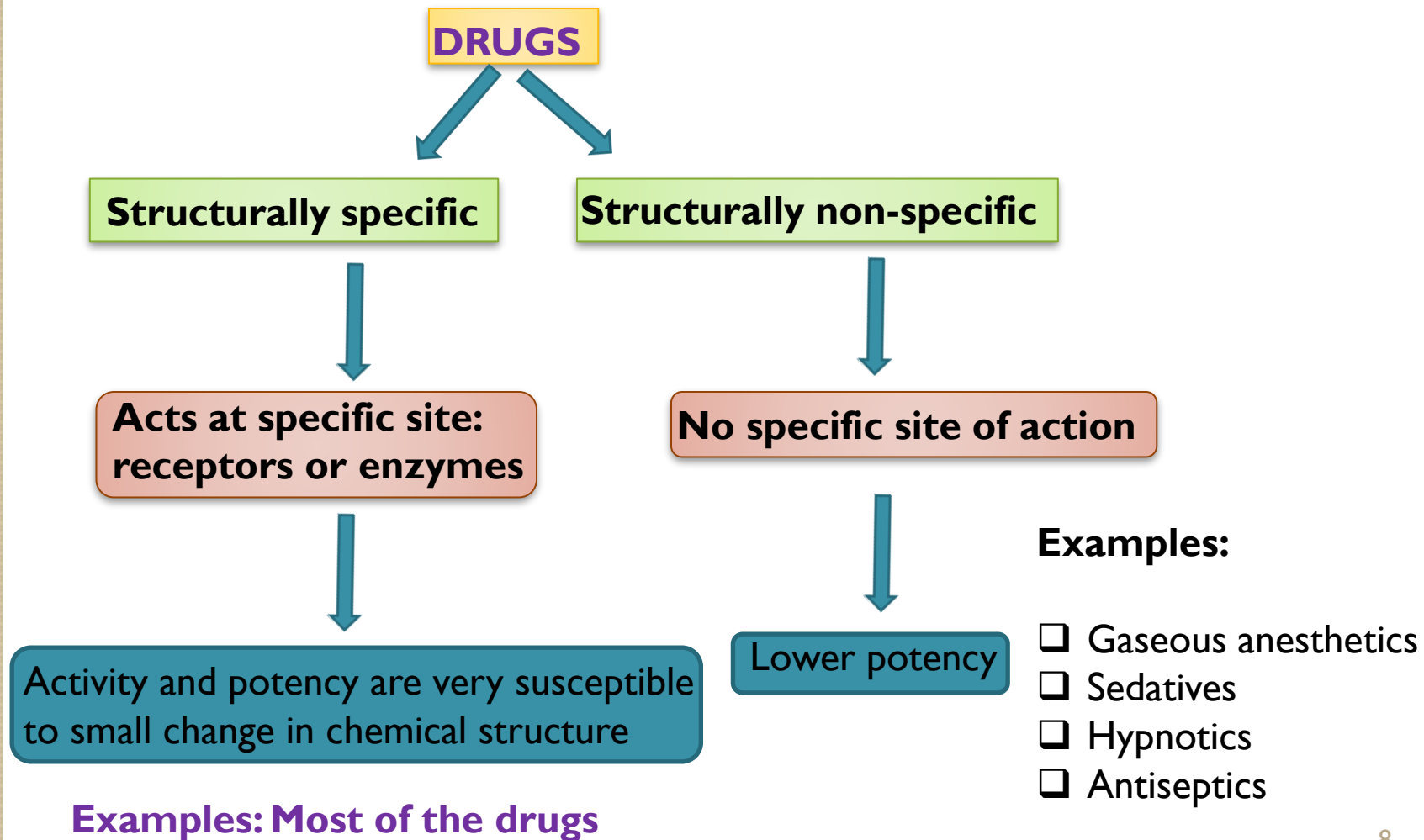**Carbutamide = Antibacterial**
    (sulphanilamide pharmacophore)
                +
    Antidiabetic
    (sulfonyl urea pharmacophore)

Tolbutamide = Antidiabetic only
        (sulfonyl urea pharmacophore)

Lead Modification

3. Structure-Activity Relationship (SAR)

DRUGS

Structurally specific

Structurally non-specific

Acts at specific site: receptors or enzymes

No specific site of action

Activity and potency are very susceptible to small change in chemical structure

Lower potency

Examples: Most of the drugs

Examples:

❏ Gaseous anesthetics
❏ Sedatives
❏ Hypnotics
❏ Antiseptics

SAR of Sulfonamides

Sulfonamide pharmacophore can show three different activities:-

1. Antibacterial; 2. Antidiabetic and 3. Diuretic

1. **Antibacterial sulphonamide**

Sulphonamide group on aniline gives Sulphanilamide which act as antibacterials.
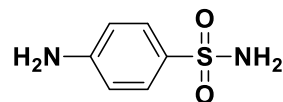
Sulphanilamide

SAR of Sulphanilamide:-

1. Amino group and sulfonyl group on benzene ring must be *para* position.

2. Amino group of aniline moiety may be removed by *in vivo*.

3. Replacement of benzene ring with any other ring decreases the antibacterial activity.

4. Amino group attached to sulfonyl moiety may be substituted to get more potent antibacterial agents.

SAR of Sulfonamides

2. Antidiabetic sulphonamide
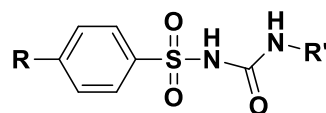
R, R' must be

alkyl/aryl/heterocyclic

3. Diuretic sulphonamide
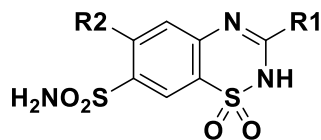
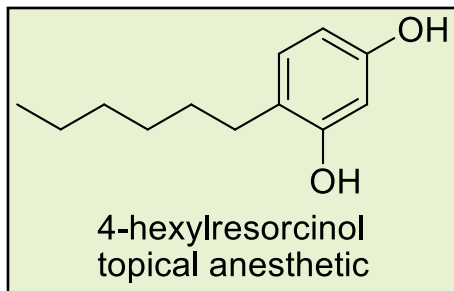
Hydrochlorthiazides
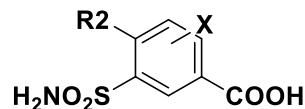
**Hydrochlorthiazides**

Lead Modification

4. Structure modification to increase potency and therapeutic index

A. Homologation

A homologous series is a group of compounds that differ by a constant unit, generally a CH_2 (Methylene) group.
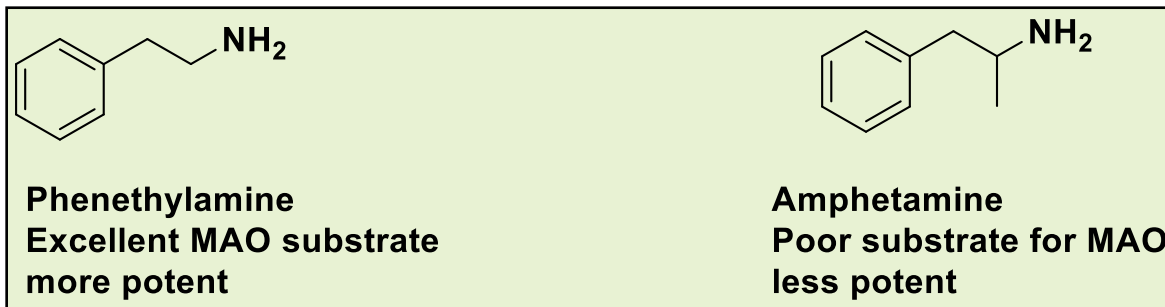

4-hexylresorcinol
topical anesthetic

✓ **Chain length up to 9 carbon atom....tolerable (optimum lipophilicity and water solubility.**

✓ **Chain length more than 9 carbon atoms… low water solubility… low bioavailability.**
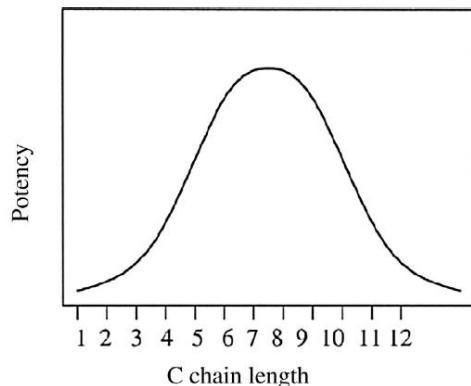
Lead Modification

B. Chain branching

❑ **Chain branching lowers the potency because the branched alkyl chain is less lipophilic than the straight alkyl chain.**

❑ **Chain branching may interfere with the receptor binding due to larger molar volume and shape.**

Phenethylamine
Excellent MAO substrate
more potent

Amphetamine
Poor substrate for MAO
less potent

C. Ring chain transformation

Affects both lipophilicity (increase) and drug metabolism (decrease).

Arecoline is more effective *in vivo*.

Arecoline

Acetylcholine
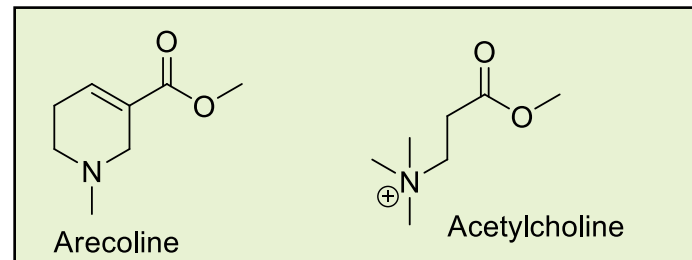
Lead Modification

D. Bioisosterism

❖ **Bioisosterism is an important lead modification approach.**

❖ **Bioisosteres are groups or substituents that have chemical or physical similarities, and which produce broadly similar biological properties.**

Importance or the use of Bioisosteres

➢ **Attenuate toxicity.**
➢ **Modify the activity of a lead.**
➢ **Alter the pharmacokinetics of lead.**
➢ **Potentiate activity.**

Two types of Bioisosteres

I. **Classical Bioisosteres.**

II. **Non-classical Bioisosteres.**

Lead Modification

I. Classical Bioisosteres

Are atoms or molecules in which the peripheral layers of electrons can be considered identical.

Subclasses:

Univalent:
CH_3 , NH_2 , OH , F , Cl
Cl, SH
Br, *i*-Pr
I, *t*-Bu

Divalent:
$-CH_2-$, -NH- , -O- , -S-
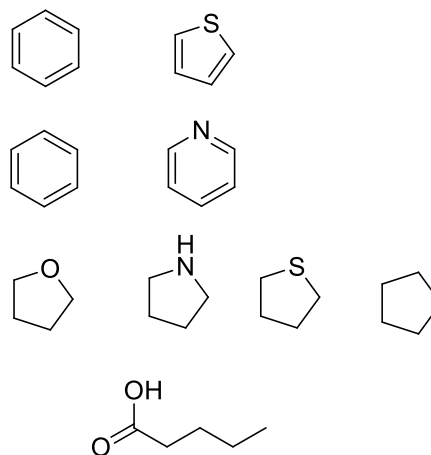$-CO-CH_2-$, -CO-NH- , -CO-O-, -CO-S-

Lead Modification

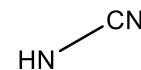## 1 Classical Bioisosteres continued……
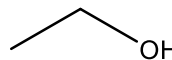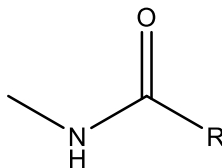
Trivalent:
   -CH= , -N=

Tetravalent:
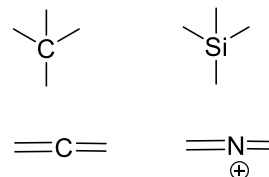
Ring equivalent:

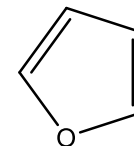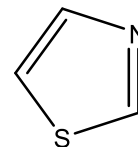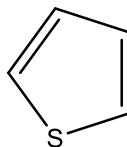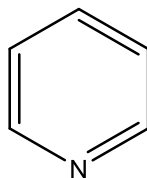# Lead Modification

II. Non-classical Bioisosteres Continued……

Hydroxyl group

Halogens

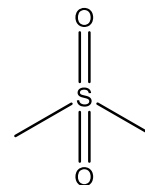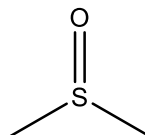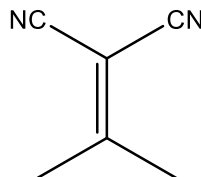X CF_3 CN $N(CN)_2$
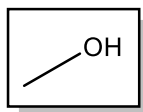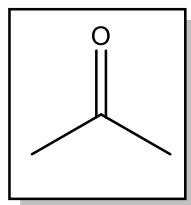
Benzene
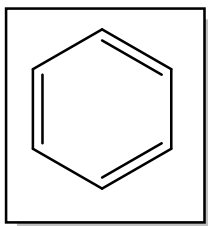
Lead Modification

II. Non-classical Bioisosteres

✓ **They do not have the same number of atoms and do not fit the steric and electronic rules of the classical isosteres.**

✓ **But produce similar biological activity.**

Examples:

Carbonyl group

Lead Modification

II. Non-classical Bioisosteres Continued……

Carboxylic acid group
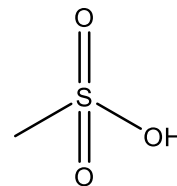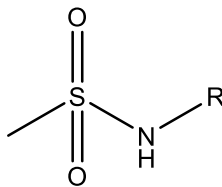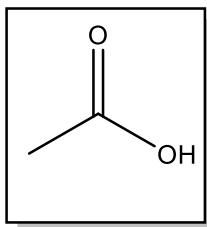
Amide group
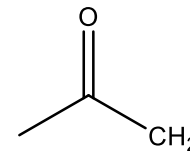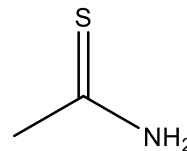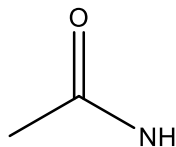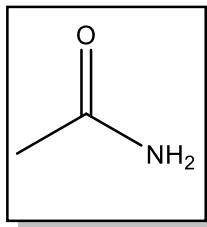
Lead Modification

E. Peptidomimetics
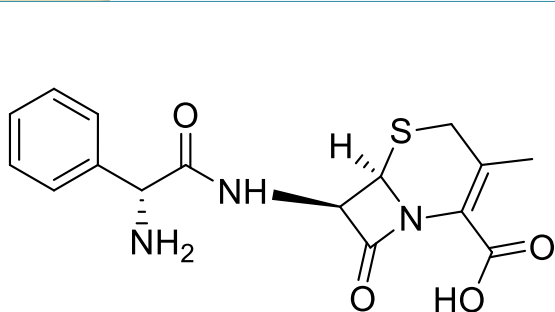
cephalexin

TRH
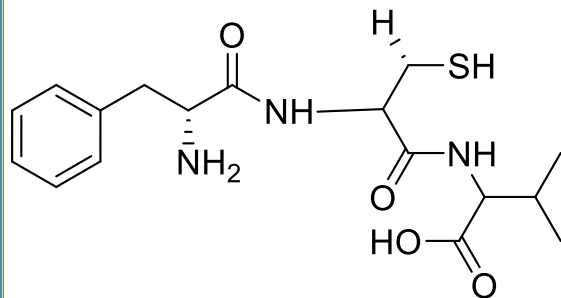
Enalapril

resembles

resembles

resembles

D-Phe-Cys-Val
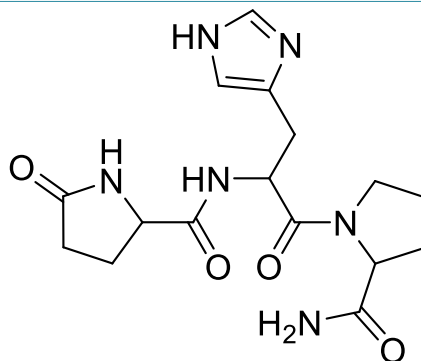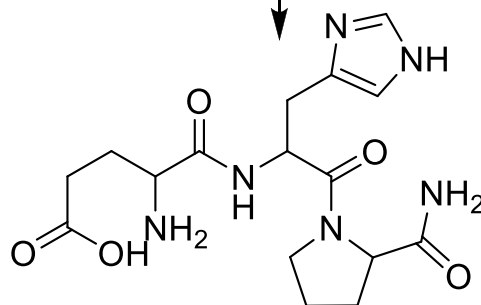
Gln-His-Pro
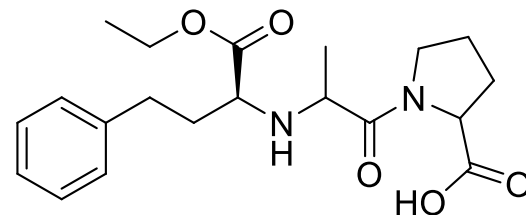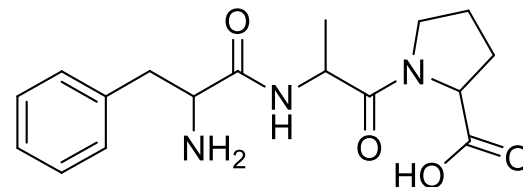
Phe-Ala-Pro

Lead Modification

5. Structure modification to increase oral bioavailability

Factors affecting oral bioavailability:

1. Lipophilicity.

2. Effect of ionization.

3. Physico-chemical stability.

4. Biological stability:

   a. Effect of intestinal enzymes.

   b. First pass metabolism.

Lead Modification

1. **Lipophilicity.**
   Low water solubility of the compound or high lipophilicity can be a limiting factor in oral bioavailability.

✓ There is a co-relation between lipophilicity and biological activity.

✓ The orally administered drug must have moderate lipophilicity (logP = 2-5) in order to absorbed through the lipophilic mucus membrane or membrane solubility.

✓ It is recommended that one can predict the lipophilicity of the chemical compound before start synthesizing it.

✓ Hansch proposed a model of membrane to determine the lipophilicity.

✓ 1-Octanol was selected because it simulates the lipophilic membrane; relative to that in water; long saturated alkyl chain, a hydroxyl group for hydrogen bonding and sparingly soluble in water (1.7M).

Lead Modification

✓ **As a measure of lipophilicity, Hansch proposed 'partition coefficient, *P*' a measure of the solubility of compound in 1-octanol versus water.**

$$P = \frac{[\text{Compound}]_{\text{oct}}}{[\text{Compound}]_{\text{aq}}\ (1-\alpha)}$$

Where,

   P **= partition coefficient**

   α **= degree of dissociation of the compound in water calculated from**

   ionization constant.

oct = 1-Octanol

 aq = aqueous buffer or water.

In general, ionization makes the compound more soluble in water.

Experimentally, log *P* can be determined by 'shake flask method'.

Lead Modification

Substituent or fragment constant

	Aliphatic	Aromatic		Aliphatic	Aromatic
-F	-0.38	0.37	C_6H_4	1.67	1.67
-Cl	0.06	0.94	-H	0.23	0.23
-Br	0.20	1.09	-NH-	-2.15	-1.03
-I	0.59	1.35	-OH	-1.64	-0.44
-NO_2	-1.16	-0.03	-NH_2	-1.54	-1.00
-O-	-1.82	-0.61	-SH	-0.23	0.62
-S-	-0.79	0.03	-CONH-	-2.71	-1.81
-CH_3	0.89	0.89	-COOH	-1.11	-0.03
-CH_2-	0.66	0.66	-$CONH_2$	-2.18	-1.26
-CH<	0.43	0.43	-CN	-1.27	-0.34
>C<	0.20	0.20	-CO-	-1.90	-1.09
C_6H_5	1.90	1.90	-CO_2-	-1.49	-0.56

Lead Modification

Calculate the log *P* of Ibuprofen
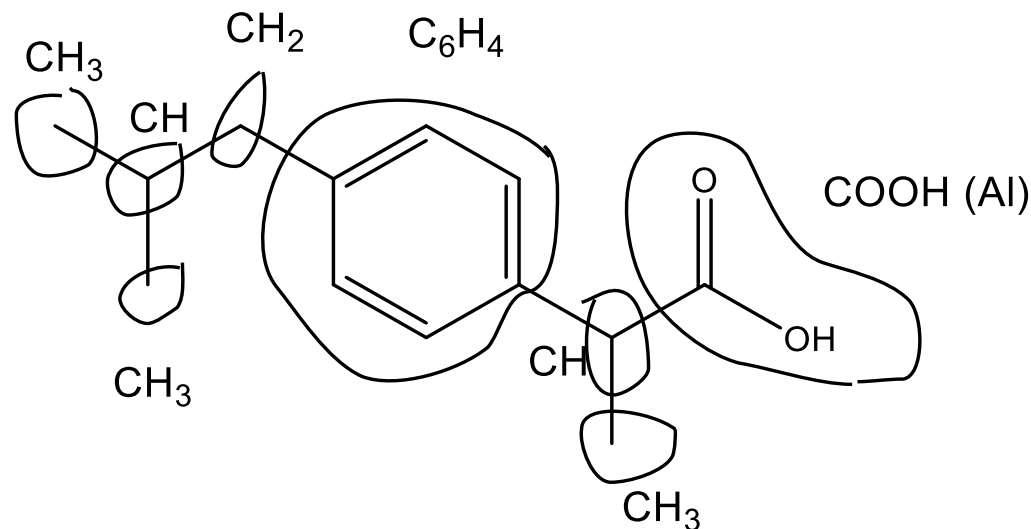
LogP = 3CH$_3$ + 2CH + 1CH$_2$ + C$_6$H$_4$ + COOH (Al) – 2 branches

= 3 * 0.89 + 2 * 0.43 + 0.66 + 1.67 – 1.11 – 2 * 0.2

= 4.35

Lead Modification

✓ **Because of the problems associated with ionization of compounds, the term log D (the log of the distribution coefficient) is used to describe the lipophilicity of the ionizable compound.**

✓ **log D describes the log P of ionizable compound at a particular pH.**

Example: **Metoprolol (change in log D as a function of pH)**

Metoprolol
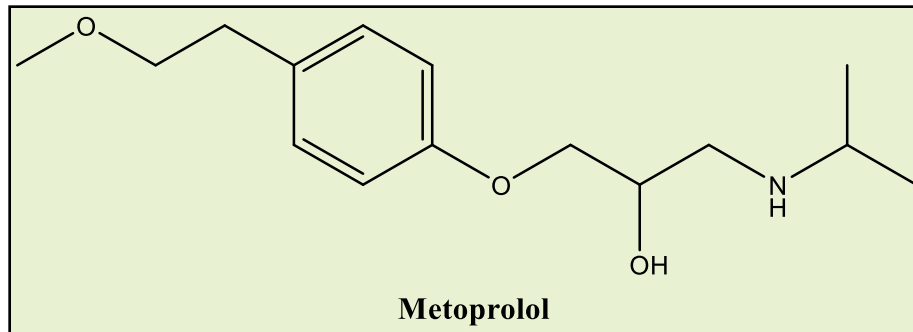
Log D	pH
-1.31	2.0
0.12	7.5
1.73	10.0

❑ **log P of unionizable compound is independent of pH.**

Lead Modification

✓ **To predict the lipophilicity of the whole molecule, we must know the lipophilicity of substituents in it.**

✓ **The lipophilicity substituent constant 'π' is calculated using the equation**

$$\pi = \log P_X - \log P_H$$

Where,

π = Lipophilicity substituent constant.
P_X = Partition coefficient for the compound with substituent 'X'.
P_H = Partition coefficient for the parent molecule (X = H).

❑ π constant is **additive** and **constitutive**

Additive = Multiple substituents exert an influence equal to the sum of the individual substituents.
Constitutive = Effect of a substituent may differ depending on the molecule.

Lead Modification

Factors affecting lipophilicity

❑ Branching: log P will be lowered by 0.2 per branch.

❑ Inductive effect of electron withdrawing groups.

❑ Resonance effect: It will affect the possibility of H-bonding with aqueous phase.

H$_3$C—OH
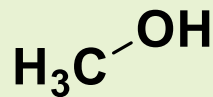
Methanol

Methanol is more polar, less lipophilic than phenol

OH
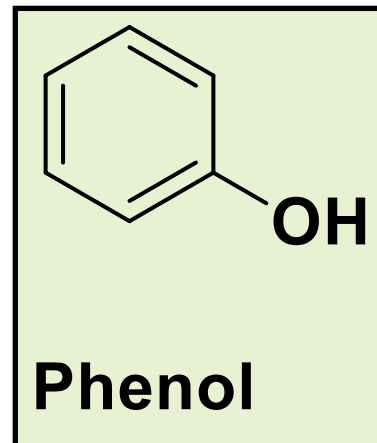
Phenol

Lead Modification

2. Effect of ionization

Extent of ionization of drugs may affect the following:

- ❑ **Lipophilicity.**

- ❑ **Oral availability.**

- ❑ **Receptor-drug interaction.**

- ❑ **Excretion.**

- ❑ **Distribution.**

Lead Modification

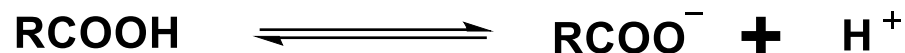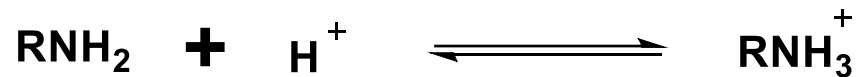**An equilibrium is possible between the ionized and unionized or neutral form depends on pH of medium and pK_a of ionizable group.**

$$RNH_2 \; + \; H^+ \; \rightleftharpoons \; RNH_3^+$$

$$RCOOH \; \rightleftharpoons \; RCOO^- \; + \; H^+$$

When pH = pKa, 50% molecules ionize and only the unionized form will be able to cross the membrane and absorbed in GIT.

The equilibrium will be reestablished to generate unionized drug again for further absorption.

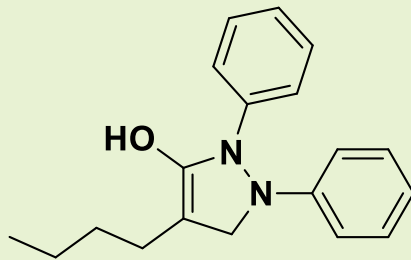**The ionized form of the drugs will interact with the target receptor.**

In order to modify the ionization, electron donating or withdrawing groups can be added to lead molecule to modify pKa.

Lead Modification

Example-1:

Uricosuric effect of phenylbutazone and Sulfinpyrazone

Uricosuric activity: **Increases the excretion of uric acid through urine**
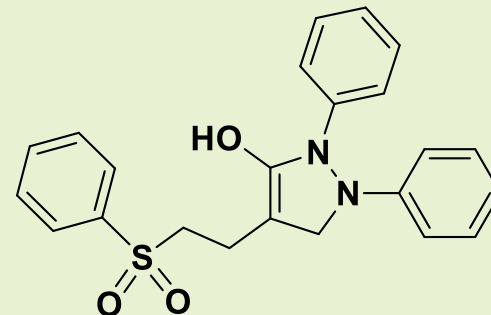

Phenylbutazone
pKa = 4.5
Active in anionic form and found less concentration in urine
low effect as uricosuric agent; But used to treat inflammation

Sulfinpyrazone
pKa = 2.8
better ionized in urine; Anionic form blocks reabsorption of uric acid by renal tubule. Better uricosuric agent to treat gout.
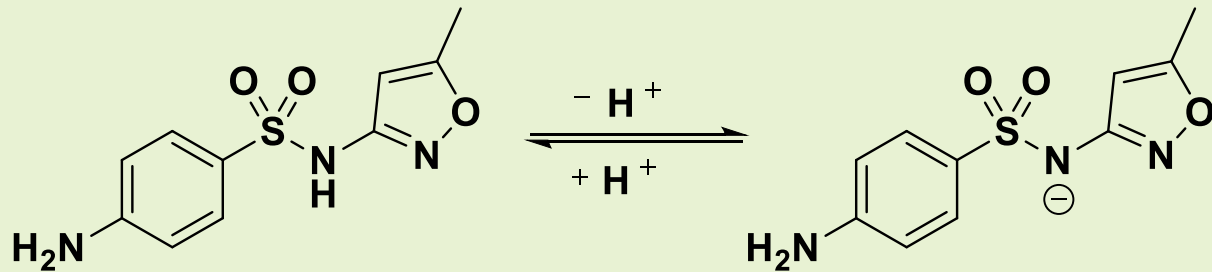**20 times more potent than phenylbutazone**

Lead Modification

Example-2:

Ionization equilibrium of Sulfamethoxazole

**unionized form of sulphamethoxazole
important for getting into the bacterial cell
(important for pharmacokinetics)**

**Ionized form of sulphamethoxazole
important for enzyme interaction
(important for pharmacodynamics)**

Lead Modification

Other Properties Influencing Oral Bioavailability

"**Lipinski's rule of five**" **to improve oral bioavailability during lead modification.**

The rule of five states that the orally administered drug must not have:

- ❑ **A molecular weight > 500 Dalton**

- ❑ **LogP > 5**

- ❑ **H-bond donor > 5 (expressed as the sum of OH and NH)**

- ❑ **H-bond acceptor > 10 (expressed as the sum of O and N)**

Exception of the rule of five:
- • **Antibiotics**
- • **Antifungals**
- • **Vitamines**
- • **Cardiac glycosides**

Reason for exception:
These drugs have active transporters to carry them across membrane.

Lead Modification

"**Veber rule**" **to improve oral bioavailability, drug must have**:

- ❑ **Rotatable bonds ≤ 10**

- ❑ **Polar surface area $\leq 140\,A^{\circ 2}$**

- ❑ **Total hydrogen bond count ≤ 12**

Drugs targeting CNS should have:

- ✓ **H-bond donor ≤ 3**

- ✓ **H-bond acceptor ≤ 6**

Lead Modification

"Ajay findings" to cross the blood-brain barrier and for CNS activity.

- ❑ **If the molecular weight, the degree of branching, the number of rotatable bonds or the number of H-bond acceptors increased, the compound will less likely to be CNS active.**

- ❑ **If the aromatic density, the number of H-bond donors or log *P* is increased, the compound is more likely to be CNS active.**

Recommended Books
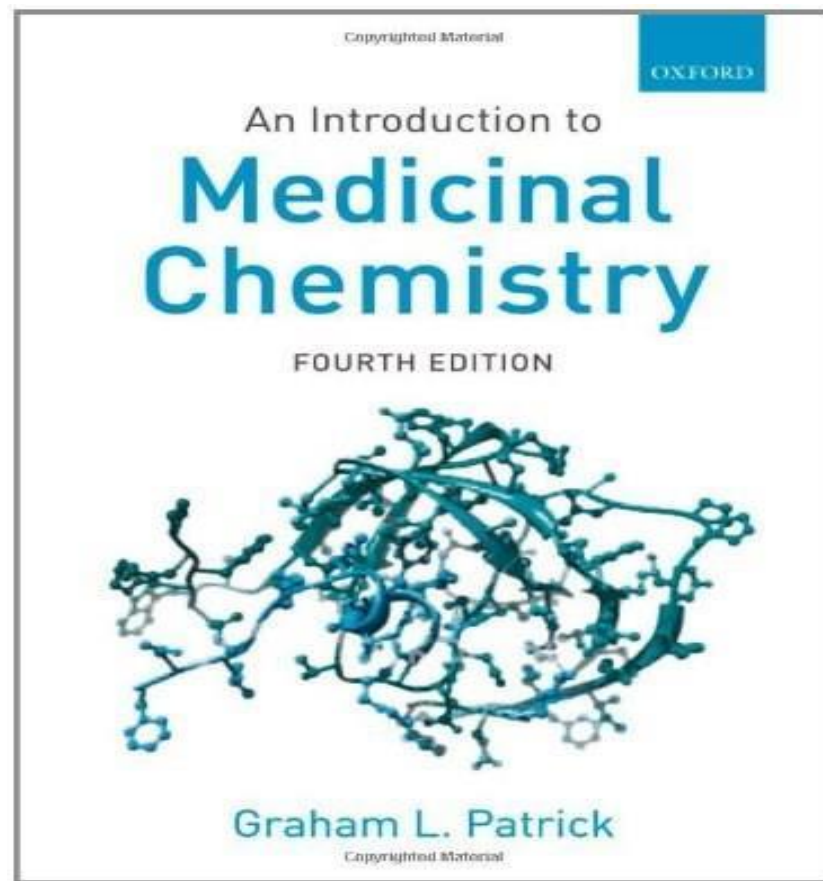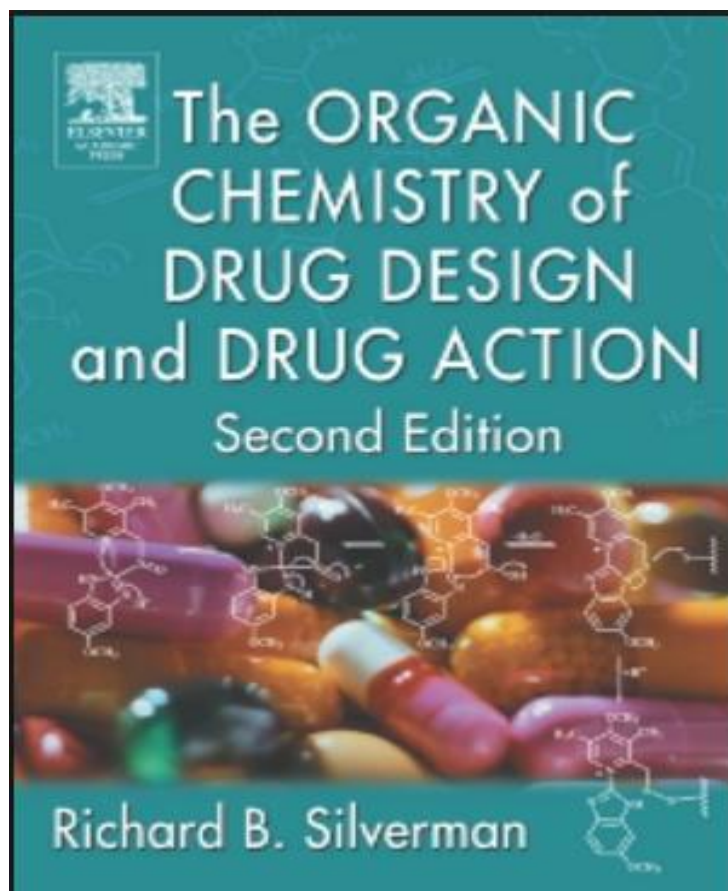
1. The organic chemistry of drug design by Richard B. Silverman. Second edition, Elsevier, 2004.

2. An introduction to Medicinal Chemistry by Graham L. Patrick. Fourth edition, Oxford, 2009.