INTRODUCTION

Principles of drug designing

- Improving the selectivity
- Increasing the selectivity
- Reduce side effects
- Arrangement functional groups and identification of a pharmacophore

WHAT IS QSAR ?

- A QSAR is a mathematical relationship between a biological activity of a molecular system and its geometric and chemical characteristics.

- QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these “rules” can be used to evaluate the activity of new compounds.

QSAR involves the derivation of mathematical formula which relates the biological activities of a group of compounds to their measurable physicochemical parameters. These parameters have major influence on the drug's activity.QSAR derived equation take the general form:

- Biological activity = function (parameters)
  - Activity is expressed as log(1/c). C is the minimum concentration required to cause a defined biological response

Physicochemical Parameters

Various parameters used in QSAR studies are:

- **Hydrophobicity:** partition coefficient, π-substitution constant
- **Steric Parameters:** Taft's constant, verloop steric parameter
- **Electronic Parameter:** Hammet constant, dipole moment

HYDROPHOBICITY

- Hydrophobic character of a drug is crucial to how easily it crosses the cell membrane and may also important in receptor interactions.

- Hydrophobicity of a drug is measured experimentally by testing the drugs relative distribution is known as partition coefficient

Partition coefficient:

Partition coefficient P usually expressed as logP

It is defined as

$$p = \frac{(X)ocatanol}{(X)aqueous}$$

- P is a measure of the relative affinity of a molecule for the lipid and aqueous phase in the absence of ionization.

- 1-Octanol is a most frequently used lipid phase in pharmaceutical research

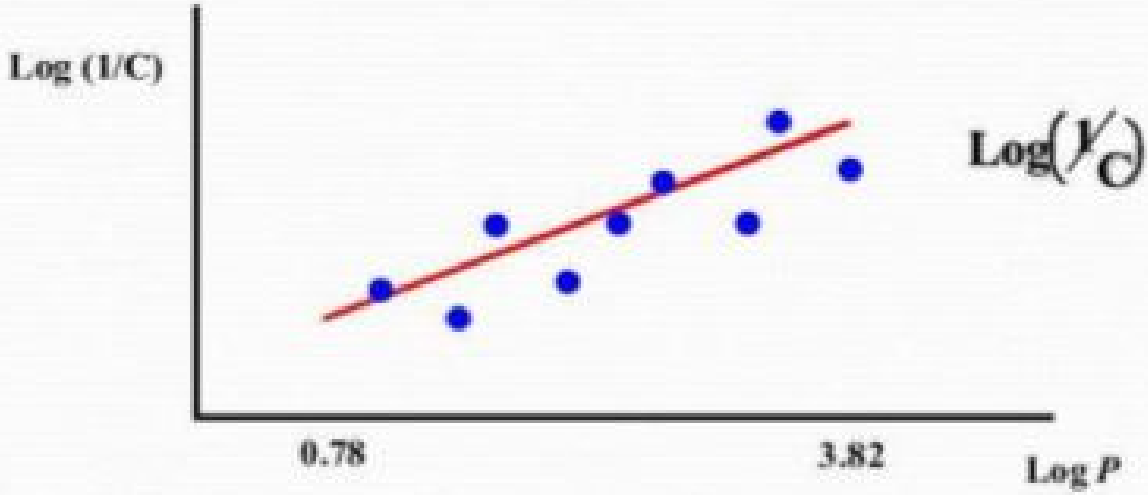
LogP for a molecule can be calculated from a sum of fragmental or atom based terms plus various corrections.

$$\text{LogP} = \Sigma \text{ fragments} + \Sigma \text{ corrections}$$

Relationship between LogP and Log1/C

- **Activity of drugs is often related to *P***

  e.g. binding of drugs to serum albumin
  (straight line - limited range of log *P*)

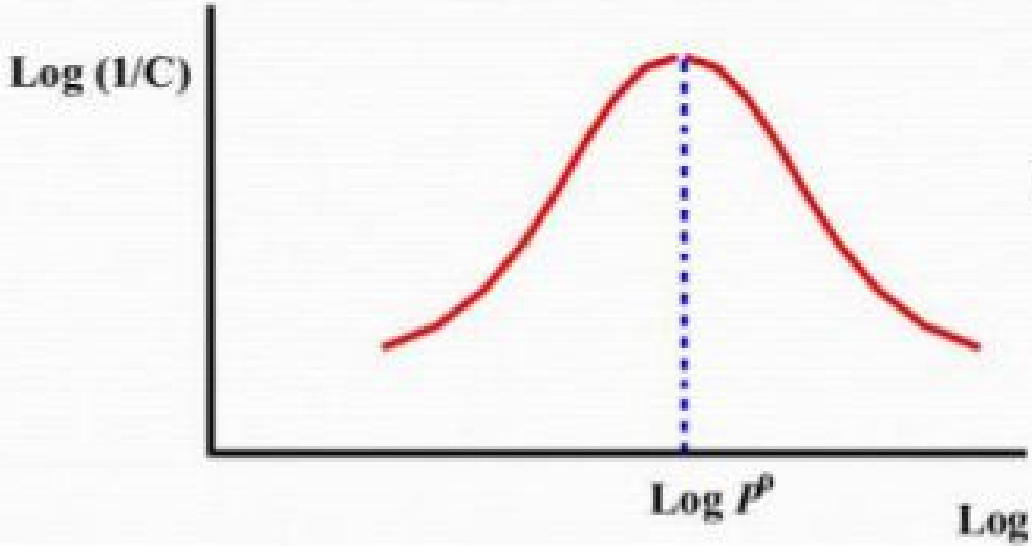


$$\text{Log}\left(\frac{1}{C}\right) = k1 \log P + k2$$

- **Binding increases as log *P* increases**
- **Binding is greater for hydrophobic drugs**

Example 2 General anaesthetic activity of ethers

(parabolic curve - larger range of log *P* values)



$$\text{Log}\left(\frac{1}{C}\right) = -k1\,(\log P)^2 + k2\log P + k3$$

Optimum value of log *P* for anaesthetic activity = log P^o

π-substituent constant

The π-substituent constant defined by hansch and co-workers by the following equation.

Partition coefficient can be calculated by knowing the contribution that various substituent , is known as substituent hydrophobicity constant.

$$\pi x = \log Px - \log PH$$

A positive π value indicates that the π substituent has a higher hydrophobicity than hydrogen

A negative π value indicates that the π substituent has a lower hydrophobicity than hydrogen and the drug favors the aqueous phase.

π identify specific regions of the molecule which might interact with hydrophobic regions in the binding sites.

ELECTRONIC EFFECT

- The electronic effect of various substituent will clearly have an effect on drug ionization and polarity.

- Have an effect on how easily drug can pass through the cell membrane or how strongly it can interact with a binding site.

The Hammett constant (σ)

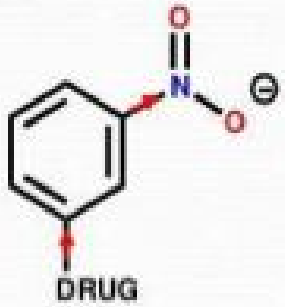
$$sx = \log (Kx/K \text{ benzoic})$$

Hammett constant takes into account both resonance and inductive effects; thus, the value depends on whether the substituent is *para or meta* substituted

- -*ortho* not measured due to steric effects

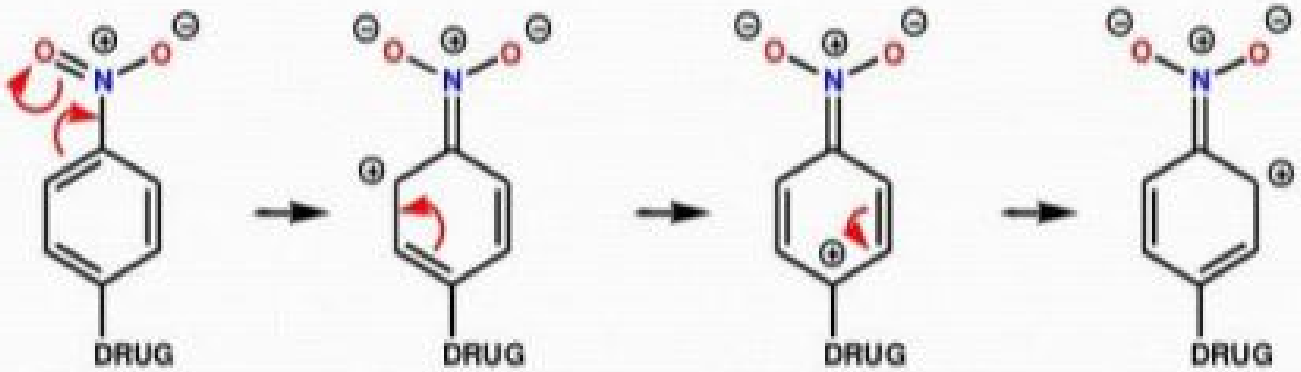
EXAMPLES: $\sigma_p (NO_2) = 0.78$ $\sigma_m (NO_2) = 0.71$

meta-Substitution



e-withdrawing (inductive effect only)

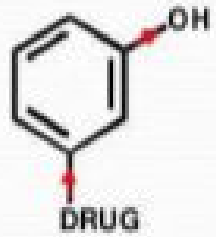
para-Substitution



e-withdrawing (inductive + resonance effects)

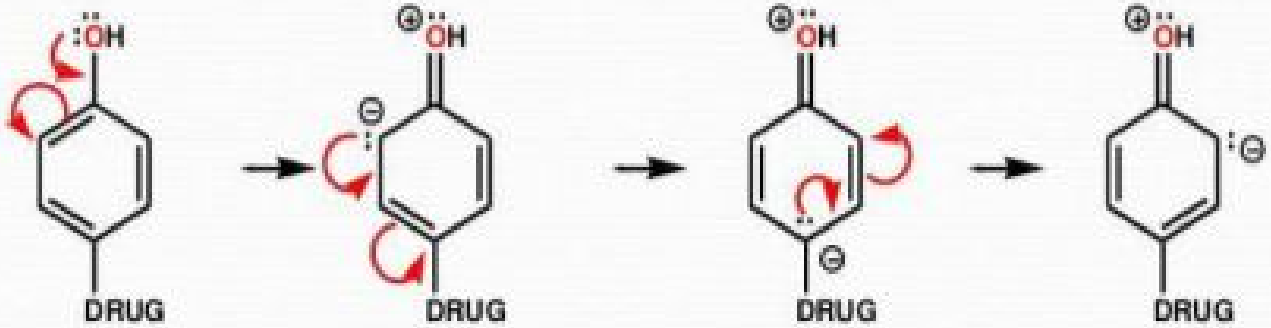
EXAMPLES: σ_m (OH) = 0.12 σ_p (OH) = –0.37

meta-Substitution



e-withdrawing (inductive effect only)

para-Substitution



e-donating by resonance more important than inductive effect

STERIC SUBSTITUTION CONSTANT

It is a measure of the bulkiness of the group it represents and it effects on the closeness of contact between the drug and receptor site

Bulky substituent may help to orient a drug property for maximum binding and increase activity.

Taft's steric factor (Es)

It is measure by the comparing the rate of hydrolysis of substituted aliphatic esters against a standard ester under acidic condition

$$E_s = \log k_x - \log k_o$$

k_x represents the rate of hydrolysis of a substituted ester

k_o represents the rate of hydrolysis of the parent ester

Molar refractivity (MR)

measure of the volume occupied by an atom or group--equation includes the MW, density, and the index of refraction

Verloop steric parameter

- Calculated by software STERIMOL
- Gives dimensions of substituent from the standard bond angle, van der waals radii, bond length.