FACULTY OF ENGINEERING AND TECHNOLOGY

Department of Biotechnology

What is QSAR

- Quantitative Structure Activity Relationship(QSAR) is a set of methods that tries to find a mathematical relationship between a set of descriptors of molecules and their activity.

- The descriptors can be experimentally or computationally derived. Using regression analysis, one can extract a mathematical relationship between chemical descriptors and activity.

INTRODUCTION

- The QSAR approach attempts to identify and quantify the physicochemical properties of a drug and to see whether any of these properties has an effect on the drug's biological activity.
- such a relationship holds true, an equation can be drawn up which quantifies the relationship and allows the medicinal chemist to say with some confidence that the properties has an important role in the distribution or mechanism of the drug.
- It also allows the medicinal chemist some level of prediction. By quantifying physicochemical properties, it should be possible to calculate in advance what the biological activity of a novel analogue might be.

- The formulation of thousands of equations using QSAR methodology attests to a validation of its concepts and its utility in the elucidation of the mechanism of action of drugs at the molecular level and a more complete understanding of physicochemical phenomena such as hydrophobicity.
- **Crum-Brown** and **Fraser** expressed that the physiological action of a substance was a function of its chemical composition and constitution.

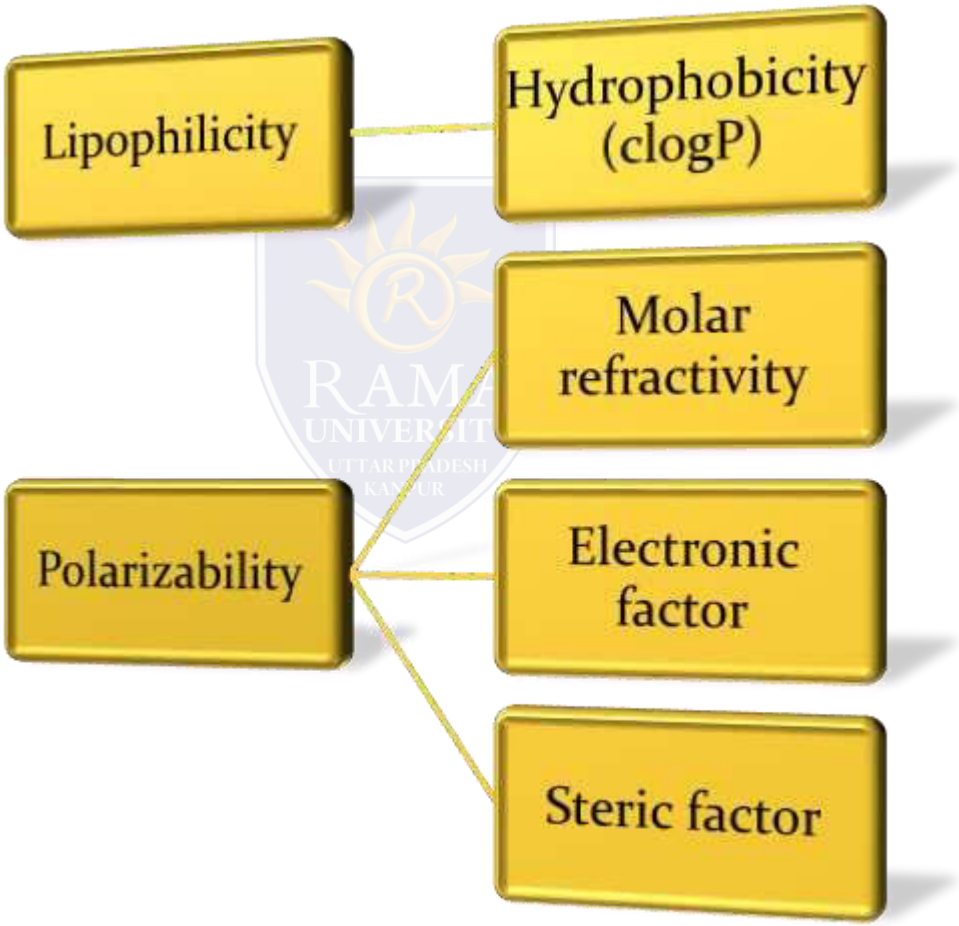
Advantages

1. Allows the medicinal chemist to target efforts on analogues which should have improved activity and thus, decreases the number of analogues which have to be made.
2. If an analogue is discovered which does not fit the equation, it implies that some other feature is important and provides a lead for further development.

What are Physicochemical Properties

- They refer to any structural, physical, or chemical property of a drug.
- The drug will have a large number of such properties ✓and it would be a very difficult task to quantify and relate them all to biological activity at the same time.
- A simple more practical approach is to consider one or ✓two physicochemical properties of the drug and to vary these while attempting to keep other properties constant. This is not as simple as it sounds, since it is ✓not always possible to vary one property without affecting another.
- The QSAR study then considers how the hydrophobic, electronic, and steric properties of the substituents affect biological activity.

Physicochemical descriptors



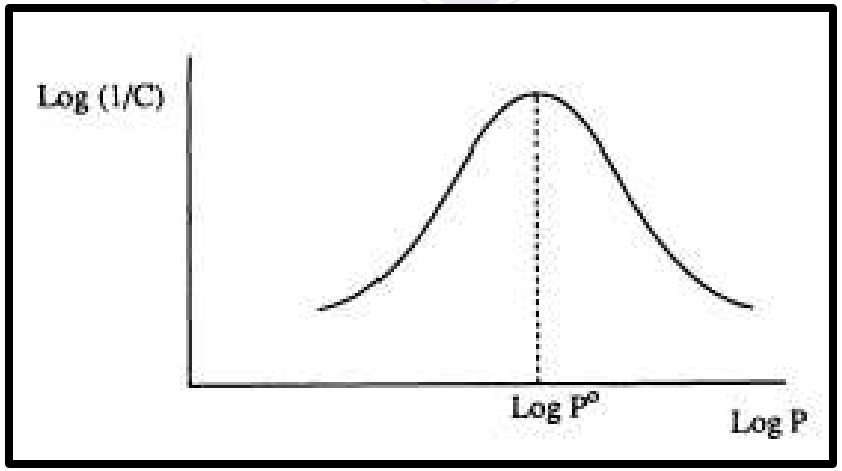
Hydrophobicity/Lipophilicity

- Hydrophobic character of a drug is crucial to how easily it crosses cell membranes and may also be important in receptor interactions. Changing substituents on a drug may well have significant effects on its hydrophobic character and hence its biological activity.
- The partition coefficient (P)

p=Concentration of drug in octanol/Concentration of drug in aqueous solution

- **The hydrophobic character of a drug can be measured experimentally by testing the drug's relative distribution in an octanol/water mixture. Hydrophobic molecules will prefer to dissolve in the octanol layer of this two-phase system, whereas hydrophilic molecules will prefer the aqueous layer. The relative distribution**

- Hydrophobic compounds will have a high P value, whereas hydrophilic compounds will have a low P value.
- By plotting these P values against the biological activity of these drugs, it is possible to see if there is any relationship between the two properties.
- The graph is drawn by plotting log (1/C) versus log P.



- The scale of numbers involved in measuring C and P usually covers several factors of ten and so the

  allows manageable numbers.

- Where the range of the logP values is restricted to a small range (e.g. logP = 1-4), a straight-line graph is obtained showing that there is a relationship between hydrophobicity and biological activity. Such a line would have the following equation:

$$\log (1/C) = k1 \log p + k2$$

- For example, the binding of drugs to serum albumin is determined by their hydrophobicity and a study of 40 compounds resulted in the following equation:

$$\log (1/C) = 0.75 \log P + 2.30$$

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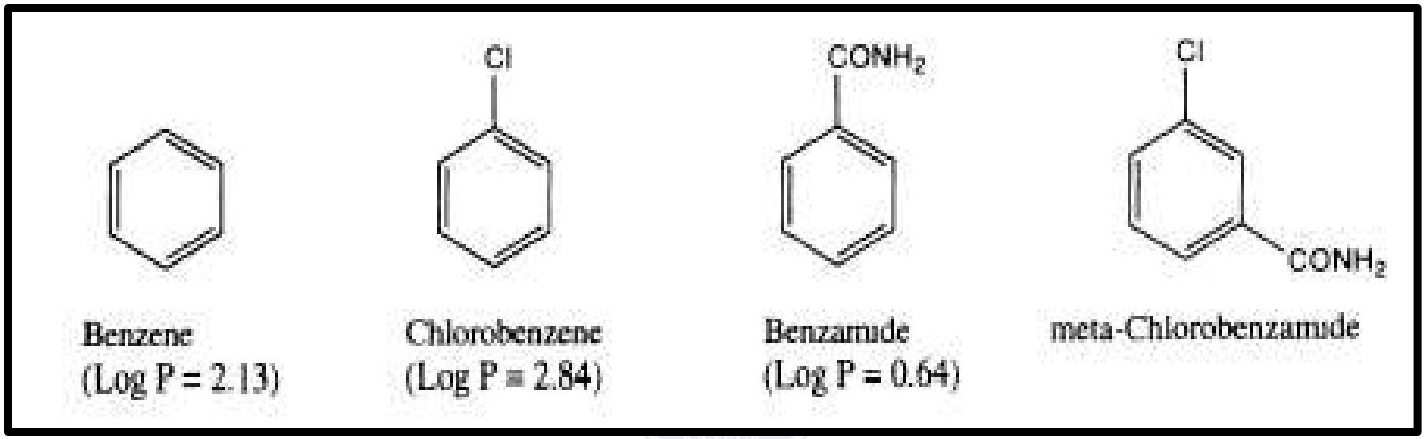
- The equation shows that serum albumin binding increases as log P increases. In other" words, hydrophobic drugs bind more strongly to serum albumin than hydrophilic drugs.
- As an example of this, the cardiotonic agent was found to produce 'bright visions' in some patients, which implied that it was entering the CNS.

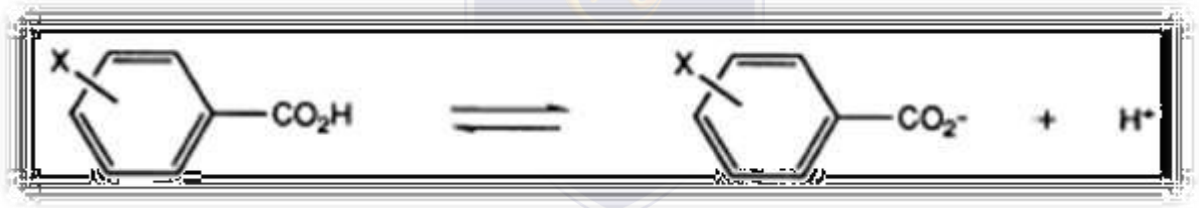


Values for log P

Electronic Effects

- The electronic effects of various substituents will clearly have an effect on a drug's ionization or polarity. This in turn may have an effect on how easily a drug can pass through cell membranes or how strongly it can bind to a receptor.
- As far as substituents on an aromatic ring are concerned, the measure used is known as the Hammett substitution constant .
- The Hammett substitution constant ( ) is a measure of the electron withdrawing or electron donating ability of a substituent and has been determined by measuring the dissociation of a series of substituted benzoic acids compared to the dissociation of benzoic acid itself.

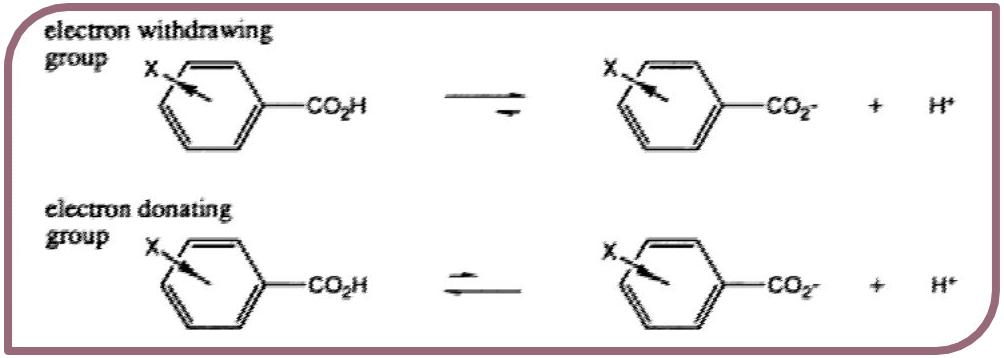
- Benzoic acid is a weak acid and only partially ionizes in water. An equilibrium is set up between the ionized and non-ionized forms.



Ionization of benzoic acid

- Dissociation constant (K_H)=[$PhCOO^-$]/[PhCOOH]

- When a substituent is present on the aromatic ring, this equilibrium is affected. Electron withdrawing groups, such as a nitro group, result in the aromatic ring having a stronger electron withdrawing and stabilizing influence on the carboxylate anion.
- The equilibrium will therefore shift more to the ionized form such that the substituted benzoic acid is a stronger acid and has a larger *Kx value*.



Conti...

- If the substituent X is an electron donating group such as an alkyl group, then the aromatic ring is less able to stabilize the carboxylate ion. The equilibrium shifts to the left and a weaker acid is obtained with a smaller *Kx value.*
- The Hammett substituent constant ( ) for a particular substituent (X) is defined by the following equation:

$$x = \log K_x/K_H = \log K_x - \log K_H$$

- Benzoic acids containing electron withdrawing substituents will have larger *Kx values* than benzoic acid itself (KH) and therefore the value of x for an electron withdrawing substituent will be positive. Substituents such as Cl, CN, or CF3 have positive a values.

- Benzoic acids containing electron donating substituents will have smaller *Kx values* than benzoic acid itself and hence the value of x for an electron donating substituent will be negative.
- Substituents such as Me, Et, and Bu' have negative a values. The Hammett substituent constant for H will be zero.
- The Hammett constant takes into account both resonance and inductive effects. Therefore, the value of a for a particular substituent will depend on whether the substituent is meta or para.

Steric Parameters

- These are absolutely necessary for a drug molecule to engage into a viable interaction either with a drug receptor or with an enzyme.
- Obviously, this essentially demands certain specific criteria that a drug molecule must fulfil as: bulk, size and shape of the drug. The bulky substituent more or less serve as a shield that eventually hinders the possible and feasible interaction taking place between a drug and a receptor.
- The quantitation of steric effects is complex at best and challenging in all other situations, particularly at the molecular level.

Molar Refractivity (MR)

- Molar refractivity (MR)is usually designated as a simple measure of the volume occupied either by an individual atom or a cluster (group) of atoms.
- It is one of the most widely used steric parameter.

where, n = Index of refraction,

MW = Molecular Weight,

d = Density,

MW/d = Volume and

n^2-1/n^2+2 =Correction factor (i.e., how easily the substituent can undergo polarization)

$$MR = \frac{(n^2-1)}{(n^2+2)} \times \frac{MW}{d}$$

- Molar refractivity is specifically significant in a situation when the substituent possesses either π electron or lone pairs of electrons.

- It incorporate a Polarizability component that may describe cohesion and is related to London dispersion forces.
- The failure of the MR descriptor to adequately address three-dimensional shape issues led to Verloop‘s development of sterimol parameters.

Verloop Sterimol Parameter

- The unique revelation and wisdom of a latest computer researched programme termed as sterimol has indeed helped a long way in measuring the steric factor to a reasonably correct extent. It essentially aids in the calculation of desired steric substituent values (Verloop steric parameters) based on various standard physical parameters, such as : Vander Waals radii, bond lengths, bond angles, and ultimately the proposed most likely conformations for the substituent under examination.
- It is, however, pertinent to mention here that unlike the Taft's steric factor (Es) the Verloop steric parameters may be measured conveniently and accurately for any substituent.

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