1. QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR)

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INTRODUCTION

• 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.
PARAMETERS

- The parameter is the measure of the potential contribution of its group to a particular property of the parent drug.

Various parameters used in QSAR studies are
1. Lipophilic parameters: partition coefficient, $\pi$-substitution constant
2. Polarizability parameters: molar refractivity, parachor
3. Electronic parameters: Hammet constant, dipole moment.
4. Steric parameters: Taft’s constant.
5. Miscellaneous parameters: molecular weight, geometric parameters.
LIPOPHILIC PARAMETERS

- Lipophilicity is partitioning of the compound between an aqueous and non-aqueous phase.

**Partition coefficient:**
- \( P = \frac{[\text{drug}] \text{ in octanol}}{[\text{drug}] \text{ in water}} \)
- Typically over a small range of log \( P \), e.g. 1-4, a straight line is obtained
  
  \[ \log \frac{1}{C} = 0.75 \log P + 2.30 \]

- If graph is extended to very high log \( P \) values, then get a parabolic curve
  
  \[ \log \frac{1}{C} = -k_1 (\log P)^2 + k_2 \log P + k_3 \]

- When \( P \) small, dominated by \( \log P \) term
- When \( P \) large, \( \log P \) squared dominates & so activity decreases
**π-substituent constant or hydrophobic substituent constants:**

- The π-substituent constant defined by hansch and co-workers by the following equation.
  \[
  p_x = \log P_x - \log P_H
  \]
- A positive π-value indicates that the π-substituent has a higher lipophilicity than hydrogen and the drug favours the organic phase.
- A negative π-value indicates that the π-substituent has a lower lipophilicity than hydrogen and the drug favours the aqueous phase.
The Hammett constant ($\sigma$);

$$s_x = \log \left( \frac{K_x}{K_{\text{benzoic}}} \right)$$

Electron Withdrawing Groups

- Equilibrium shifts Right & $K_x > K_{\text{benzoic}}$
- Since $s_x = \log K_x - \log K_{\text{benzoic}}$, then $s$ will be positive.
- 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.
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.
  much harder to quantitate
- Examples are:
  - Taft’s steric factor (Es) (~1956), an experimental value based on rate constants
  - 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--computer program uses bond angles, van der Waals radii, bond lengths
HANSCH ANALYSIS

- Proposed that drug action could be divided into 2 stages:
  1) Transport & 2) Binding
- Each of these stages depend upon the physical and chemical properties of the drug.
- \( \log \frac{1}{C} = k_1P = k_2P^2 + k_3s + k_4Es + k_5 \)
- Look at size and sign for each component of the equation.
- Values of \( r \ll 0.9 \) indicate equation not reliable
- Accuracy depends on using enough analogs, accuracy of data, & choice of parameters
- Applications: used to predict the activity of an as yet unsynthesized analogue.
FREE WILSON ANALYSIS

- This method is based on the assumption that the introduction of a particular substituent at a particular molecular position, always leads to a quantitatively similar effect on biological potency of the whole molecules and expressed by the equation as
  \[ BA = \mu + \Sigma aj \]
- Application:
  - Easy to apply
  - Simple method
- The substituent which can not fulfill the principle of additivity can be recognized
- Effective when substituent constants are not available.
TOPLISSL METHOD

- This approach is completely non-mathematical and non-statistical and does not need computerization of the data.
- A Topliss scheme is a flow diagram that in a series of steps directs the medicinal chemist to produce a series of analogues, some which have greater activity than lead used to start the tree.
- There are two topliss schemes
  1. For the aromatic substituents
  2. For the aliphatic side chain substituents.

Applications:
This method can be used if synthetic route might be difficult and only a very few structures can be made in a limited time.
COMPUTER AIDED DRUG DESIGN (CADD)
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- Computers are an essential tool in the modern medicinal chemistry and are important in both drug discovery and development.

MOLECULAR MODELING:
- Molecular modeling is a general term that covers a wide range of molecular mechanics and computational chemistry techniques used to build, display, manipulate, simulate and analyze molecular structure and to calculate properties of those structures.
- Molecular modeling techniques can be divided into molecular graphics and computation chemistry.
MOLECULAR GRAPHICS

- It is the core of modeling system, providing for the visualization of molecular structure and its properties.
- In molecular modeling the data produced are converted into visual image on the computer screen by graphic packages.
- These images can be displayed in a variety of styles like space fill, stick, ball and stick etc.
- Ribbon presentation is used for large large molecules like nucleic acid and protein.
MOLECULAR MECHANICS

- In this technique the energy of structure is calculated.
- The equation used in molecular mechanics follow the law of classical physics and applies to the molecular nuclei without consideration of the electrons.
- It assumes that the total potential energy in a molecule is given by the sum of all the energies of the attractive and repulsive forces between the atoms in the structure.
- \[ E_{\text{total}} = \sum E_{\text{stretching}} + \sum E_{\text{bend}} + \sum E_{\text{torsion}} + \sum E_{\text{vdw}} + \sum E_{\text{Coulombic}} \]

Advantages:
1. Less time consuming
2. Simple to use
MOLECULAR DYNAMICS

- Molecular dynamics programs allow the modular to show the dynamic nature of the molecule by simulating the natural motion of the atom in a structure.
- The velocities of the atoms are related directly to temperature.
- Higher temperature stimulations are used to search conformational shape.
- Molecular dynamics can also be used to find minimal energy structure and conformational analysis.
  
  Ex: conformational analysis of butane
QUANTUM MECHANICS

- It is based on the realization that electrons and all material particles exhibit wave like properties.
  \[ H\Psi = E\Psi \]
- \( E\Psi \) represents the total potential and kinetic energy of all the particles in the structure.
- \( H \) is the Hamiltonium operator acting on the wave function.
- Quantum mechanical methods are suitable for calculating the following:
  1. Heat of formation
  2. Dipole moments
  3. Electrostatic potentials
  4. Bond dissociation energies
  5. Transition stage geometries and energies.
THANK YOU