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, π-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 = [drug] in octanol / [drug] in water
- Typically over a small range of log P, *e.g.* 1-4, a straight line is obtained

  e.g. log 1/C = 0.75 log P + 2.30
- If graph is extended to very high log P values, then get a parabolic curve

$$\log 1/C = - k_1 (\log P)^2 + k_2 \log P + k3$$

- 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 πvalue indicates that the πsubstituent has a higher lipophilicity than hydrogen and the drug favours the organic phase.
- A negative πvalue indicates that the πsubstituent has a lower lipophilicity than hydrogen and the drug favours the aqueous phase.

ELECTRONIC PARAMETERS

The Hammett constant(σ);

$$s_x = \log (K_x/K_{benzoic})$$

Electron Withdrawing Groups

- Equilibrium shifts Right & $K_x > K_{benzoic}$
- Since $s_x = \log K_x - \log K_{benzoic}$, 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.
- $\text{Log } 1/C = k_1P = k_2P^2 + k_3s + k_4Es + k_5$

- Look at size and sign for each component of the equation.
- Values of r <<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 analouge.

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.

TOPLISS 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 total= Σ Estretching + Σ Ebend + Σ Etorsion + Σ Evdw + Σ Ecoulombic

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