CHAPTER - 4

PHYSICO-CHEMICAL PARAMETERS
INTRODUCTION

Physical organic chemistry deals with characterization of the structure and prediction of the properties, the descriptors for which are usually found experimentally. If some property depends on the selected descriptors, the ordering of the structure will parallel the ordering of the properties. In other words, the structural information is coded in these properties. Therefore, good correlation of physico-chemical property with a particular set of indices may help in understanding the contribution of these invariants in determining the property.

An “ideal” set of QSAR parameters should be complete (all types of drug-biosystem interactions covered), general (not restricted to homologous series), admit interpretations (parameters well defined and physically meaningful) and re-translations of QSARs into concrete chemical structures and finally, allow the application of suitable search techniques or mathematical formalisms in order to find out which of the parameters are important and how are they connected with biological potency. Last but not the least; the parameters must be available or accessible.

Studies of Meyer and Overton, suggested inter correlations between insecticidal activity and boiling points and narcotic activity with surface
tension\textsuperscript{1,2}. This revealed that the biological activity of a drug is a function of chemical features (i.e. lipophilicity, electronic and steric properties) of the substituents and the skeleton of a drug molecule. For example, lipophilicity is the main factor governing transport distribution and metabolism of drugs in biological systems. Similarly, electronic and steric features influence the metabolism and pharmacodynamic processes of a drug. Steric crowding of substituents lead to lower the predicted activity and cooperative binding leads to increase the predicted activity. Biological activity reflects the fundamental physicochemical properties of the bioactive compounds.

A major problem in QSAR studies arises because the hydrophobic, electronic and steric effects overlap and cannot be neatly separated. The parameters which are used to obtain such correlations can be divided into

(i) those which describe mainly the physical properties of a skeleton, such as water solubility, partition coefficient, chromatographic $R_f$ values, molecular weight, surface tension etc.

(ii) those which describes the chemical properties such as dipole moment, charge densities, electron donor-acceptor properties, Hammett’s electronic constants, Taft’s steric constants etc.
Parameters which encode certain structural features and properties are needed to correlate biological activities with chemical structures in a quantitative manner. Of specific value, physico-chemical properties which are directly related to the intermolecular forces involved in the drug-receptor interaction as well as to the transport and distribution properties of drugs. In this respect hydrophobicity, polar, electronic and steric properties are most important.

In QSAR it is considered that the biological activity is connected with the physico-chemical properties. So, biological activity, which is represented in either form of C, Ki, IC₅₀, ED₅₀ and Kₘ and the physico-chemical properties, which are broadly classified into electronic, lipophilic and steric parameters, are connected with a mathematical equation. The parameters selected should be orthogonal, that is, have minimal covariance.

*Our study can be described under following major physico-chemical parameters:*

[A] Electronic parameter

[B] Lipophilic parameter

[C] Steric parameter

[D] Parachor
Electronic parameters mainly indicate the influence of polar character of the drug on its biological activity. They affect

(i) metabolism and elimination pattern of the drug

(ii) the drug-receptor interaction.

Electronic properties of molecules can be described by a wide variety of different parameters e.g. by

- Hammett $\sigma$ constants
- Field and resonance parameter, $F$ and $R$
- $pk_a$ values
- parameters derived from molecular spectroscopy
- charge transfer constants
- dipole moments
As all these parameters describe the influence of a certain group or substituent on electron density distribution, all have been used in QSAR studies. Early work examining the electronic role of substituents on rate constants was first tackled by Burckhardt and firmly established by Hammett\textsuperscript{3,4,5,6}. In 1940, \textbf{L.P. Hammett} published his book on "Physical Organic Chemistry" in which he introduced – constants as a quantitative measure of the electronic effects of substituents of aromatic ring on reaction rates and equilibria. Hammett postulated that the electronic effect of a set of substituents on different organic reactions should be similar. He selected substituted benzoic acids, $X-C_6H_4-COOH$ as the standard system to develop the numerical $\sigma$ constant scale. The most commonly used electronic parameter is Hammett substituent constant ‘$\sigma$’.

\textit{Hammett substituent constant:} Hammett electronic parameter or substituent constant, $\sigma_x$ is the electronic effect of substituent x relative to
hydrogen. $\sigma_x$ determination is based on the influence of a substituent on the ionization of benzoic acid.

$$\rho \sigma = \log K_{a(R)} - \log K_{a(I)}$$

where,

$\rho$ is the constant for a given reaction. $\sigma$ is the substituent constant and $K_a$ is the equilibrium constant (or rate constant, $K_a$) for the reaction of interest.

There are several other ways of quantifying electronic effects. For example, electronic effects can be represented as a linear combination of a field (inductive) effect, $F$ and a resonance effect, $R$:

$$\sigma = aF + bR$$

where,

$a$ and $b$ are coefficients determined from the data fitting. The use of $\sigma$ has been extended to biological. Those value may then be applied to many types of reactions as characterized by different values of the reaction constant, $\rho = 1$, by definition, for the ionization (dissociation) of benzoic acid. Where,

$$\log \left( \frac{K_x}{K_{1I}} \right) = \rho \sigma_x$$
where,

$K_H$ is the equilibrium or rate constant for the parent (unsubstituted) and $K_x$ is the equilibrium or rate constant for the derivative measured experimentally.

*Electron withdrawing groups* like $-\text{NO}_2$ increases $K_x$ and ultimately leads to a positive $\sigma$ whereas *electron donating groups* like $-\text{OCH}_3$, decreases $K_x$ and thus leads to a negative values. Substituent location is important for the value of $\sigma$. Meta and Para substituents generally correlate well whereas ortho yields poor correlations. There is greater resonance contribution of a substituent in para position and somewhat greater inductive contribution of a substituent in meta position, $\sigma$ ortho was unreliable because of its steric interaction with the adjacent core group.

In considering electronic effects, one has to differentiate between field (inductive) effects and resonance effects. Due to the characteristic features of a benzene ring, $\sigma_m$ mainly describes the inductive effect while $\sigma_p$ stands for a combination of both effects, with the resonance effect predominating. Over the past decades, many different $\sigma$ scales were developed in organic chemistry, besides $\sigma_m$ and $\sigma_p$ also $\sigma^*$ (to account for substituents which donate electrons to the aromatic ring system by direct resonance interaction), $\sigma^-$ (for corresponding acceptor substituents), $\sigma^0$
and $\sigma^n$ (normal or unexalted $\sigma$ constants), $\sigma_i$ and $\sigma_R$ (inductive and resonance contributions), etc.

In 1968, **Swain and Lupton** tried to stop the proliferation of $\sigma$ scales. They defined field and resonance components $F$ and $R$, by assuming that any set of $\sigma$ values can be expressed by a weighted combination $aF + bR$ that there is resonance contribution in the case of 4-substituted bicyclo [2.2.2] octane-carboxylic acids ($b=0$), and that there is no resonance contribution of $N^+(CH_3)_3$ substituent ($R=0$).

The substituent constant $\sigma$ is linearly dependent on $\Delta G$, the change in the free energy arising due to dissociation of benzoic acids. The reason for using the logarithm of biological response has thermodynamic origins. Here $\log K_R/K_H$ is used instead of free energy change because equilibrium constants are logarithmically related to free change ($\Delta G$) change through the Van't Hoff equation and therefore additive.

Hammett proposed that an electron withdrawing group, attached to aromatic ring of benzoic acid would increase the acid strength of the carboxyl group and greater the electron withdrawing power, the greater will be an increase in the strength. Thus electron withdrawing groups have positive values, electron donating groups have negative values and hydrogen has zero values.
In general, the Hammett equation applies to aromatic systems only for reactions in which substituent (x) and the reaction centre (y) are "insulated", so that no resonance interaction occurs between them. That is as long as ‘x’ affects ‘y’ in a fashion parallel to the way ‘x’ affects the ionization constant of the corresponding benzoic acid, the Hammett equation can be expected to hold.

Taft has formulated the parameter $\sigma^*$ to define the polar effects of substituents when the group in question does not form part of a conjugated system. It is to be used in aliphatic systems.

This polar constant is defined as:

$$\sigma^* = [\log (k/k_0)_B - \log (k/k_0)_A] \times 1/2.48$$

$log (k/k_0)_n$ refers to the hydrolysis rate constants of esters (XCH$_2$COOR) in basic solution and log $(k/k_0)_A$ to the hydrolysis of the same esters under acid conditions.

Sigma constants are position dependant. For example, $\sigma$ value for a substituent at meta position is different from that in the para position. Sigma value for ortho substituent ($\sigma_0$) cannot be calculated because of possible steric hinderance.
Hammett’s student Taft showed how the electronic effect could be separated into two numerical scales, one for the inductive and other for resonance effects of the substituents.\(^7\)

**Inductive effect** (electron withdrawing or donating) refers to the polarity produced in a molecule as a result of higher electronegativity of one atom compared to another. The carbon-hydrogen bond is used as a standard. Zero is assumed in this case. Atoms or groups, which donate electrons to carbon atom, are said to have a +I effect. Those atoms or groups, which draw electrons away from carbon atom are said to have –I effect.

**Resonance effect** occurs with para substituents and can lead to large magnitude \(\sigma\) values. The \(\sigma\) is the reaction constant indicates the influence of the electronic effect on the binding constant. If \(\sigma > 1\), then the electronic contribution of the substituent is greater than it is for the ionization of benzoic acid. If \(\sigma < 1\), then the electronic contribution of substituents is less than it is for the ionization of benzoic acid. Note that \(\sigma\) can be less than 0, indicating that the effect is opposite that occurring with respect to the ionization of the benzoic acid.
**Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO):** Quantum chemical descriptors such as net atomic changes, highest occupied molecular orbital/lowest unoccupied molecular orbital (HOMO-LUMO) energies, frontier orbital electron densities, and super delocalizabilities have been shown to correlate well with various biological activities. It gives the reactivity of the molecules. Molecules with high HOMO are more readily able to donate electrons than the molecules with low (HOMO). Thus, measuring the nucleophilicity of the molecules. Molecules with low-lying LUMO can accept electrons and so, measures the electrophilicity of the molecules.

**[B] Lipophilic Parameter**

This physico-chemical parameter has attracted so much interest in QSAR studies through naming lipophilicity (hydrophilicity) due to its direct relationship to solubility in aqueous phase, to membrane permeation and to its (merely entropic) contribution to ligand binding at the receptor site. Lipophilicity is defined by the partitioning of a compound between an aqueous and non aqueous phase. While early definitions of the partition coefficient $P$ referred to "light" and "heavy" phases (leading to complications in the case of organic solvents having higher density than water), now a days $P$ is defined as the ratio of substance concentrations in
the organic and aqueous phases of a two compartment system under equilibrium conditions; due to possible association of the solute in organic phase (dimers of carboxylic acids), partition coefficients should be measured at low concentration or P values must be extrapolated to infinite dilution of the solute in the system. Extensive studies over the last 35 years (40,000 experimental P-values in 400 different solvent systems) have failed to dislodge octanol from its secure perch 10. Largely with the initiative of Hansch, n-octanol now seems to be the organic solvent of choice and n-octanol/water has many important advantages as compared to the other system11,12:

* It is a suitable model of the lipid constituents of biological membranes, due to its long alkyl chain and the polar hydroxyl group.

* Its hydroxyl group is a hydrogen bond donor and a hydrogen bond acceptor, interacting with a large variety of polar groups of different solutes.

* Despite its lipophilic character it dissolves many more organic compounds than alkanes, cycloalkanes or aromatic solvents do.
* n-Octanol is UV-transparent over a large range, making the quantitative determination of many compounds relatively easy.

* n-Octanol has low vapour pressure, allowing reproducible measurements; on the other hand, its vapour pressure is high enough to allow its removal under mild conditions.

The combination of lipophilic chains, hydrophilic hydroxyl groups and water molecules appears to give n-octanol, properties very close to those of natural membranes and macromolecules. n-octanol-water partition coefficients are available from the Hansch data bank for a large number of drugs.

Partition coefficient is a free energy related parameter which expresses the relative free energy change occurring on moving a substituent from one phase to another. This is an additive property. It means, with the help of \( \pi \) values of the substituents, the log \( P \) value of any molecule may be calculated by simple addition.

Partition coefficient, based on octanol-water system is allowed for determination of hydrophobic substituent constants. Clearly absorption and distribution processes in biological systems are determined by the
**hydrophilic** or **hydrophobic** properties of molecules, for which the **partition coefficient**, \( P \), of a molecule is defined by:

\[
P = \frac{[\text{drug}]_{\text{octanol}}}{[\text{drug}]_{\text{water}}}
\]

By using logarithmic relationship, \( P \) becomes an additive property:

\[
\log P = \log [\text{drug}]_{\text{octanol}} - \log [\text{drug}]_{\text{water}}
\]

He defined a lipophilicity parameters \( \pi \) in the manner that Hammett \( \sigma \) constants were defined.

\[
\pi_X = \log \frac{P_{\text{substituted compound}}}{P_{\text{parent compound}}} = \sigma
\]

The hydrophobic substituent constant ‘\( \pi \)’ of a given substituent \( X \) is the difference of log \( P \) values of the substituted compound \( R-X \) and the unsubstituted compound \( R-H \).

For example,

\[
\pi \text{NO}_2 = \log P (\text{nitrobenzene}) - \log P (\text{benzene})
\]

\[
= 1.85 - 2.13
\]

\[
= -0.28
\]

The environment of a substituent has a significant influence on its chemical properties and therefore different activity contributions may be observed for the same substituent in different positions of a molecule.
The values of $\pi$ are highly position dependent. It means the $\pi$ value of a given substituent will not be same for ortho, meta or para position.

A negative value of $\pi$ implies that the substituent favours an aqueous phase while a positive value implies an organic phase as favoured by the drug distribution.

**Linear Relationship between Log P and Biological Activity:**

The first linear relationship was observed by *Meyer and Overton* who found that the narcotic activity of various organic compounds paralleled their partition coefficients. Exactly, linear relationship between lipophilicity and biological activity ($\log 1/c$) which was observed, especially for drugs eliciting specific toxic, anaesthetic, bactericidal, fungicidal activity or hemolytic properties. The straight line obtained ($y=mx+c$) when $\log P$ and $\log 1/c$ are represented by following equation: -

$$\log 1/c = a \log P + b$$

From such relationship, the biological activity decreases as the lipophilicity increases.

**Non-Linear Relationship between Log P and Biological Activity:**

Linear relationship between lipophilicity and biological activity only apply to certain range of lipophilicity. If lipophilicity exceeds a definite limit, a more or less sharp decrease of biological activity results for each
series of compounds and each type of biological activity. In linear equation, the lipophilicity limits are still beyond the ranges of lipophilicity. If there were no optimum lipophilicity in each series, compounds with infinite biological activity would result if only their lipophilicity were high enough.

In series of compounds, where biological activity is dependent mainly upon lipophilicity, one cannot go on increasing the biological activity indefinitely by increasing lipophilicity of the compound. Activity rises to a maximum (logP₀) and then declines.

**Figure 1.** Parabolic relationship between biological activity (log1/c) and partition coefficient (log P₀).

P₀ = The optimum value for the partition coefficient in the congeneric series under investigation.

This remains constant for that particular series.
The main reasons for the decrease in the biological activity beyond a certain range of lipophilicity include:-

(i) Because of the high lipophilicity of the drug molecule, the compound becomes so lipid soluble that it no longer can circulate in the bloodstream but merely becomes 'glued' to the first lipid membrane or macromolecule with which it comes in contact. While very polar compounds are so insoluble in organic phases that they cannot cross lipid membranes and will remain in the first aqueous phase. Hence only compounds of intermediate lipophilicity will be able to cross lipophilic as well as hydrophilic barriers to reach their target.

(ii) Ariens postulated that hydrophobic interactions between the drug side chains and a polar amino acids (like leucine, isoleucine and phenylalanine) are responsible for nonlinear effects in the protein-binding of drugs. Higher the protein-binding lower will be effective concentration of the drug.
Figure 2. Linear and parabolic Hansch plots.

The linear correlation (A) shows the dose of substituted penicillins curing 50% of mice infected with *Staphylococcus aureus*, versus the sum of the pi values of the substituents. The parabolic curve (B) is the bactericidal concentration of aliphatic fatty acids versus their partition coefficients. Parabolic dependence of activity upon lipophilicity in many equations is denoted by including $\pi^2$ or $(\log P)^2$. 
\[ \log \frac{1}{c} = -0.44 \left( \log P \right)^2 + 1.58 \log P + 1.93(\pm 0.24) \]

The combination of above type of equation with other physico-chemical parameters accounts for the non linear dependence of drug transport on lipophilicity as well as for specific hydrophobic, polar, electronic and steric interaction at the receptor.

In general, hydrophobic binding of drugs to a complementary structure will lead to an increase in the biological activity as long as the hydrophobic binding site is large enough to bind this part of the molecule. If the size of the molecule surpasses the size of the binding area, no further increase in activity will result from a further increase in lipophilicity.

[C] Steric Parameters

Steric features of the drug markedly affect the drug – receptor interactions reflecting the change in the onset and duration of biological action. The bulky substituent also delays the detachment of drug from the receptor and its leads to late onset and long duration of action.

On the guidelines provided by L.P.Hammett, a numerical scale Es for the steric effects of substituents was proposed by Hammett’s student, Taft in 1956. Various parameters are used to describe the steric features of
the substituents. The most common is Taft $E_s$ constant\textsuperscript{13}, which is derived from the acid hydrolysis of aliphatic esters.

**Taft Steric Substituent Constant:** The constant, $E_s$, depends on the fact that acid hydrolysis is determined almost completely by steric factors, is defined as

$$E_s = \log \left( \frac{K}{K_0} \right)_A$$

where,

$K = $ Ester hydrolysis rate constant for substituted compound.

$K_0 = $ Ester hydrolysis rate constant for methyl derivative.

‘$A$’ represents acid hydrolysis.

This parameter is useful for studying intramolecular steric effects, particular in reactions where the substituent is near the reaction center.

Normally, $E_s$ is standardized to the methyl group so that $E_s$ for $\text{CH}_3$ group is equal to zero. However it is possible to standardize this parameter to hydrogen i.e. $E_s (H) = 0$ and thereafter adding 1.24 to every additional methyl group. The greater the positive value of $E_s$ the greater is the steric effect, affecting intramolecular and/or intermolecular hinderance to drug – receptor interactions.
Other parameters like molar refractivity (MR), Van der Waals radii and molecular weight can be used to express steric features of the substituents.

**Molar Refractivity, (MR):**

One of the most widely used steric parameters is molar refraction (MR), which has been aptly described parameter by Tute\(^{14}\). Originally proposed by Pauling and Pressman as a parameter for the correlation of dispersion forces involved in the binding of antigen to antibodies. Now determined from the Lorentz- Lorentz equation where refraction index, \(n\), the molecular weight, MW and the density of a crystal, \(d\):

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

Since refractive index doesn’t change significantly for organic molecules, the term is dominated by MW/density i.e. Volume. Larger MW, larger the steric effect and greater the density, the smaller the steric effect (the molecules tend to pack better). A smaller MR for the same MW indicates stronger interactions in the crystal (larger density indicates that the packing is better due to stronger interactions). MR can also be considered as crude steric parameters, characterizing bulk (but not shape) of the molecule or substituent. The coefficients with MR terms challenge
interpretation, although extensive experience with this parameter suggests that a negative coefficient implies steric hindrance at that site and a positive coefficient attests to either dipolar interactions in that vicinity or anchoring of a ligand in an opportune position for interaction\textsuperscript{15}.

**Verloop Steric Parameters:**

The failure of the MR descriptor to adequately address three-dimensional shape issues led to Verloop's development of STERIMOL parameters\textsuperscript{16}, which define the steric constraints of a given substituent along several fixed axes. Five parameters were deemed necessary to define shape: $L$, $B_1$, $B_2$, $B_3$, and $B_4$. $L$ represents the length of a substituent along the axis of a bond between the parent molecule and the substituent; $B_1$ to $B_4$ represent four different width parameters. However, the high degree of collinearity between $B_1$, $B_2$, and $B_3$ and the large number of training set members needed to establish the statistical validity of this group of parameters led to their demise in QSAR studies. Verloop subsequently established the adequacy of just three parameters for QSAR analysis: a slightly modified length $L$, a minimum width $B_1$, and a maximum width $B_5$ that is orthogonal to $L$\textsuperscript{17}. The use of these insightful parameters has done much to enhance correlations with biological activities. Recent
analysis in laboratory has established that in many cases, B1 alone is superior to Taft Es and a combination of B1 and B5 can adequately replace Es\textsuperscript{18}.

**[D]. Parachor \( [P] \)**

A steric parameter is defined as a molar volume \( V \), which has been corrected for forces of intermolecular attraction by multiplying with the fourth root of surface tension. Mc Gowan developed this parameter which principally relates to the volume.

\[
[P] = VY^{1/4} = MY^{1/4}/D
\]

where,
M=molecular weight
D= density.

**[E]. Polarizability Parameters**

Molar volume \( MV \), molar refractivity \( MR \), and parachor \( PA \) are theoretically and practically closely interrelated (equations 1-3; \( MW= \) molecular weight, \( Q= \) density, \( n= \) refractivity index, \( Y= \) surface tension)

\[
MV = MW/Q .................................................. (1)
\]

\[
MR = MV. \frac{n^2 - 1}{n^2 + 2} ............................................. (2)
\]

\[
PA = MV. Y^{1/4} .................................................. (3)
\]

Molar volume itself is not strictly additive, but the corrected volume parameters \( MR \) and \( PA \) are additive constitutive molecular properties,
like logP and Hammett σ parameters. While molar refractivity has attracted much attention, molar volume and parachor have only rarely been used in QSAR studies.

[F] Chromatographic Parameters

Besides π (for a substituent) and log P (for a molecule), other parameters that describe lipophilicity of the drug molecule include, partition coefficient $R_M$ value, molecular connectivity index (it also describes steric properties) and Van der Waals $V_w$.

In 1965, Boyee and Milborrow suggested the use of $R_M$ value from reversed-phase thin layer chromatography (TLC) as alternative lipophilicity parameters in QSAR$^{19,20}$.

$$R_M = \log \left( \frac{1}{R_f} - 1 \right)$$

However, $R_M$ values cannot be regarded as true equilibrium.

Many advantages are associated with the use of $R_M$ values instead of the use of partition coefficients.

These include:

(a) Only minute quantity is required.

(b) Since the impurities do not affect $R_f$ values, the compounds need not to be pure.
(c) Since the determination of $R_f$ value is more quicker and less tedious process, a number of compounds can be investigated simultaneously on the same place.

(d) $R_f$ value can be calculated for both very polar and very lipophilic substances with equal ease by using a wide range of solvent mixtures.

While the most prominent disadvantages of chromatographic method are:

(a) the sensitivity of $R_f$ values to the experimental conditions.

(b) Chromatographic behavior of drug is not identical to the drug partitioning in a biological system.

(c) Large changes due to ionization or/and H-bonding may cause departure from linearity.

[G] **Structural Parameters**

These are truly structural descriptors because they are based only on the two-dimensional representation of a chemical structure. The most widely known descriptors are those that were originally proposed by Randic$^{21}$ and extensively developed by Kier and Hall$^{22}$. The strength of this approach is that the required information is embedded in the hydrogen-
suppressed framework and thus no experimental measurements are needed to define **Molecular Connectivity Index** ($\chi$), it indicates the degree of branching in a given structure. Since, branched isomers of molecule differ in their properties, the arrangement of substructure in the given molecule must be responsible for it. Molecular connectivity describes molecular substructure in topological terms. Correlation of the physical properties with the variation in the structure depends not only on number of atoms in the structure but also upon arrangement of these atoms. Since, size and shape of the molecule determines many of the physical parameters that govern the biological activity of drug, molecular connectivity index helps to quantify the effect of size and shape on the biological response.

For calculation of connectivity index, the structural formula of the compound is written as skeletal formula without the hydrogen atoms. It is known as hydrogen- suppressed graph. Then the valence number ($\delta_i$) of atoms attached to each atom is indicated. Such valence numbers of adjacent atoms are multiplied and the bond contribution is calculated by taking the reciprocal square root of the product $\delta_i\delta_j$. Thus the molecular connectivity index for the given compound is calculated by following formula:

$$
\chi = \sum (\delta_i\delta_j)^{1/2}
$$
**[H]. Indicator Parameters**

Indicator variables (sometimes called *dummy variables* or de novo constants) are used in linear multiple regression analysis to account for certain features which cannot be described by continuous variables.

In QSAR equations they normally describe a certain structural element, be it a substituent or another molecular fragment. The role of indicator variable can be of diverse type. Sometimes it defines an important substructure (pharmacophore), ortho interaction, a substitute for steric parameter and a separator between two isomers, different parent skeletons, hydrogen bond donor and acceptor properties etc. It may also act as "molecular book-keeping" where the variation in similar type of biological activity of large and diverse sets of congeners is explained by one equation.

For the particular group or substituent it is taken as 1 and for all such cases where that group or substituent is absent it is taken as 0. The negative sign before coefficient of indicator parameter, in the regression equation indicates the lowering of potency due to that particular substituent for which the value of indicator parameter is taken as one, if it has positive sign this signifies that the drug with that particular group at
specific position will enhanced potency and will help as in designing new series of drug.

**Concept of Outliers**

An outlier\(^23\) may lead to a deeper insight into drug action and may even allow one to arrive at new lead compounds\(^24\) thus, outliers may provide very valuable information. Hansch called them "a blessing in disguise". The detection and follow up of outliers is an important aspect of the QSAR methodology.

Outlier is an observation which does not appear to confirm with the rest of observations. It should be explored and analysis repeated with the outliers omitted. If the outliers are simply due to an adequate parameter space it may be helpful to plot the deviation from regression line versus several molecular parameters. If such plot show regularities, the outliers may then be fitted by appropriate changes of parameters, care is in order here, however allow only for such changes which are meaningful.

If a large percentage of the training series does not fit one can no longer speak of outliers. In such cases the QSAR analysis obviously was a failure and has to be repeated. Under no circumstances can a practice be accepted where a larger portion of compounds omitted without any good
reason in order to make the equation fit to data. This does not refer to dividing a series into sub group.

In the present thesis the different types of physico-chemical parameters were taken such as lyophilicity ($\pi$), molar refractivity (MR), Field effect (F), resonance effect (R) and Hammett’s constant ($\sigma$) which are described completely in the present chapter.
REFERENCES


2. Overton E., Studien Uber die Narkose, Fischer, Jena, Germany, 1901.


