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An Importance and advancement of QSAR parameters in modern drug design: A Review

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ABSTRACT
From the last 30 years QSAR study become important to help in designing of drugs. Many software and hardware are used in discovery of drugs. QSAR techniques employ powerful computers to generate large data bases result. Quantities structure activity relationship and quantative structure property relationship is essentially computerised statistical methods which help to explain the observed variance in the biological effect of certain classes of compound. It assumes that a biological activity of certain compound is a function of various physico chemical properties are favourable to the concern activity. QSAR involve themathematical and statistical analysis of SAR data which help to minimize the molecular modification. The ultimate objective of the present study is to understand the force governing the activity of a particular compound. QSAR is thus a scientific achievement and an economic necessity to reduce empiricism in drug designing. The purpose of this study is to describe the techniques like ANN, multiple linearanalysis, partial least square method. The study further extent the types of QSAR like 1D , 2D, 3D,4D,5D etc used in designing of molecule with the help of different software. QSAR is thus a scientific achievement and an economic necessity to reduce an empiricism in drug design to ensure that every drug synthesized and pharmacologically tested should be as meaningful as possible. The uses of different parameter are important to calculate biological activity of molecule.

Key words: QSAR, Drug design, QSAR PARAMETER, MLR, ANN, Free energy model, Quantum mechanical method.

INTRODUCTION

The introduction of Hansch method in 1964 enables chemist to describe SAR study in quantative terms.[1]during past decade, QSAR started to develop from a more advance stage. Various methods used in QSAR analysis can be explain that how the molecule is biological active or not. The activity of the molecules depends upon the different parameters like hydration energy , molecular volume of molecule, parachore, Log P values etc.[2] Physical organic chemistry deals with characterisation of the structure and prediction of the properties, the descriptor for which are usually found experimentally. If some property depends on the set of selective descriptor,[3] the ordering of the structure will parallel the ordering of properties. In other term the structure information is coded in these properties. The good correlation of physico chemical properties with a particular set of indices may help in understanding the contribution of these invariants in determining the property.[4]

QSAR PARAMETERS

Mainly three types of physico chemical parameters are used in qsar study. Hydrophobic parameters, electronic paramerter, steric paramerter.[5]Hydrophobic parameter like partition coefficients log P , Pi substituent's constant , Rm chromatographic parameters log Rm, solubility parameter δ, elution time in HPLC log K and parachore [P] are used in study.[6-7]

Electronicparameters can be divided in two parts 1. Experimental parameters 2.Theoretical parameters. Experimental parameters are generally Ionization constant Pka and sigma substituent's constants σ and σ^2 and spectrochemical shifts are described in term of ppm. Resonance effect R and field effect F and Ionization potential calculated in term of I.[8-9]

The theoretical quantum mechanical indices[10] MO indices are generally studied as atomic charge densities ϵ, atomic net charge q, QT, Q, σ etc. and superdelocalisibilityS_r^n and energy of molecular orbital'sby E_{LEMO} andE_{HOMO} and other parameters like N, NH, $F^{[A]}$ are also used to describe and calculate the data for result . The third type of parameters are steric parameters like Taft's steric substituent's constants ES andvandersWaals radii ϒ and inter atomic distances B, L , molar refractivity MR and molar volume MV are used for calculation of value to obtained biological

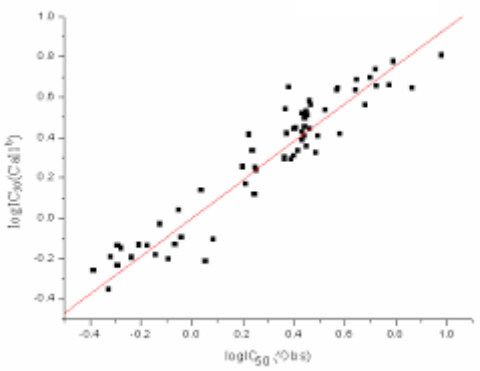
activity.[11]Biological activity reflects the fundamental physico chemical properties of the bioactive compound. The lipophilicity,polarity,chargesdistributions are main parameter to calculate biological activity.
Major problems in QSAR study arises because hydrophobic, electronic and steric effect overlap and cannot be separated easily. The parameters which are used to obtain such relation can be divided in to two parts. Those which describe mainly the physical properties of Skelton such as water solubility partition coefficient, chromatographic Rf value, molecular weight, surface tension etc. And another parameters which describe the chemical properties like charge densities, dipole moments, electron donor acceptor properties, Hammetts constant, Taft's steric constant.[12-13]

QSAR METHODS
There are various methods to calculate the qsar parameters. The introduction the hansch methods.In 1964 enables chemist to describe the SAR studied in quantative term. There are various methods like free energy model and other statistical methods, Pattern recognition, topological methods[14],quantum mechanical methods and molecular modelling[15] are used for qsar analysis. The free energy model is used to describe the Hansch method for linear free energy relationship calculation and other method is free wilson mathematical model.
The statistical methods are discriminate analysis, principal component analysis, Factor analysis, cluster analysis and combined multivariate analysis. There are two way to get a quantative information about SAR, one may use QSAR methods based on linear free energy relationship which relate the biological activity of a molecule with contributions from various free energy related physicochemical parameter of the substituent's. In other approach mathematical model are used other than linear free energy relationship.

SUBSTITUENT CONSTANT
When any dose of drug is given to patients than the molecules change its confirmation from Site of administration to site of action. Each confirmation has its differentenergy. The pharmacokinetics and pharmacodynamics property are based on Lipophilic (Log P)[16], electronic sigma and steric featureEs of the drug molecule. The biological activity BA can be calculated by the equation

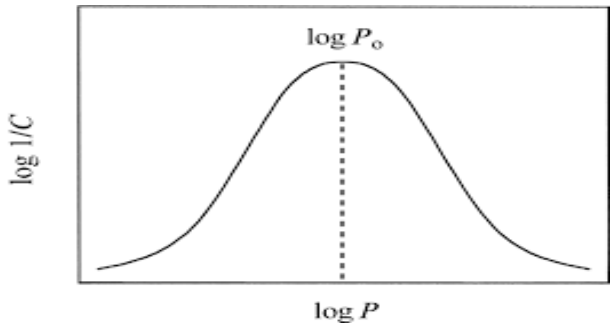
Log (BA)= a logP + b Sigma +c Es+d
Where a, b, c and d are the numerical values.

LINEAR RELATIONSHIP BETWEEN LOG P AND BIOLOGICAL ACTIVITY
Meyer and Overtonproposed first linear relationship who find that the narcotics activity of various organic compounds paralleled there oil water partition coefficients.[17]Exactly linear relationship between lipophilicity and biological activity (log 1/c)[18] is frequently observed , especially for the binding of drugs by proteins, for drugs eliciting unspecific toxic, anaesthetic, bactericidal, fungicidal , narcotic or hemolytic properties. The straight line obtained (y= mx+c) when log P and log1/c are plotted.
Log1/c= a logP+b
In such a linear relationship, the biological activity increases as the lipophilicity increases.



NON- LINEAR RELATIONSHIP BETWEEN LOG P AND BIOLOGICAL ACTIVITY
Linear relationship between lipophilicity and biological activity apply to certain range of lipophilocity. If lipophilicity exceeds a definite limit, a more or less Sharpedecrees of biological activity result for each series of compounds and each type of biological activity. In linear equations lipophilicity limits are still beyond the ranges of optimum lipophilicity. If

there were no optimum lipophilicity in each series, compound 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 can not go on increasing the biological activity indefinitely by increasing lipophilicity of the compound. Activity rises to a maximum (log Po) and then decline.



CHROMATOGRAPHIC PARAMETERS

Other parameter Rm is used to describe the lipophilicity of drug molecule. In 1965 Boyce and milborrow suggested the use of Rm value[19] from reverse phase thin layer chromatography (TLC)
as alternate lipophilicity parameter in QSAR.

$$\mathbf{Rm = \log (1/Rf\ -1)}$$

However Rm values cannot be regarded as true equilibrium parameters. Usually silica gel plates are impregnated with liquid paraffin's , silicone oil, ethyl oleate or n -octanol as stationary phase. While mobile phase may consist of mixture of polar solvents like methonol, ethynolaceton with water or aqueous buffer solution. There are many advantages of using Rm value instead of partition coefficient.

OTHER PARAMETERS RELATED TO LIPOPHILICITY

For defining the lipophilicity other parameters like solubility parameter[20] and dissolution rate constant are used. Yalkowasky and Valvani have correlated molecular surface area[21] with the lipophilicity of polar compounds. Other physico chemical parameter like molar volume MV, molecular refrectivityMR[22], vanderwaals volume Vw and parachore PA can also be correlated with lipophilicity.[23-24]

$M = Mw/d$ where Mw is molecular weight and d is density.

$$MR = \frac{n2-1\ MW}{n2+2\ \ d}$$ where n is refractive index.

$PA = r^{1/4}\ MW/d$ where r is surface tension

Molarrefractivity is a volume term, but is also proportional to electron polarisibility[25]. Hence its calculation in qsar is difficult. If the confirmation dependent steric effect are eliminated molar refractivity may be used as a measure of dispersion and dipole induced dipole forces. Molar refractivity and parachore may be regarded as corrected molar volumes. The lipophilicity however not be correlated with molar volume, molar refractivity and parachore if polar compound are induced.

The capacity factor (log k) determined by HPLC is an indicator of lipophilicity.

$$K = \frac{tr - t_o}{t_o}$$

wheretr and t_o are retention time of solute and unretened compound for a series eluted by
methanol–water mobile phase. Centrifugal counter cartography is used to measure partition coefficient.

ELECTRONICS PARAMETER

The polar charecters of drug are calculated by electronic paramete[26]. σ_m is called hammett constant for meta substituents derived from ionisation of benzoic acid.[27]$\sigma_p$is known is hammett constant for para substituents derived from ionisation of benzoic acid. σ_p- Hammet constant used when there is direct conjugation between substituents and

reaction centre derived from aniline and phenols. σ $P^+$is calledH.C. brown constant derived from solvolysis of di methyl phenyl carbonyl chlorides. σ_1 constant describing solely polar effect. σ_R constant describing solely mesmeric effect[28].σ* is Taft's polar substituents constants[29] derived from hydrolysis of aliphatic esters. Sigma parameter is haemolytic constant for substituents interacting with a free radical reaction. F and R are field and resonance components derived for linear combination of σ_m and σ_p values. The main commonly used electronic parameter is Hammett substituents constantswhich can be obtained from the dissociation constant K_X and K_H of the benzoic acid.

$$\sigma = \log Kx - \log KH = \log(Kx/KH) = pKaH - pKax$$

The substituents constant σis depends on Delta G; free energy arises due to dissociation of benzoic acid. Hammetts told that and electron withdrawing group attached to aromatic ring of benzoic acid would enhance the acid strength of carboxylic group.

STERIC SUBSTITUTENTS CONSTANTS

Drug receptor interaction is depending on steric features of drug. Bulky group delayed the activity of drug receptor interaction[30]. L.P. Hammett studentTaft's proposed a numerical scale Es in 1956 to determine the drug receptor interaction based of favourable confirmation of the molecule. Many parameters are used to describe the steric value of the substituents. The taft's constant Es is derived from the acid hydrolysis of aliphatic esters.

$$\text{Log } (K/ko) = Es$$

Where K=Rate of acid hydrolysis of substituted esters and Ko=rate of hydrolysis of parents esters. For explaining the steric feature the molecular refractivity, Vander Waals radii, molecular weight and molecular connectivity indices can be used.[31]More value of Es greater is the steric effect affecting intramolecular or intermolecular hindrance to drug receptor interaction.

Molar refractivity is the other steric parameter based on lorentz equation.

$$MR = \frac{(n2-1)\ MW}{(n2+2)\ d}$$

Where n= index of refration at the sodium D line
mw= molecular wt of compound.
d= density.
Larger the value of MR greeter the steric contribution.
If the substance is in liquid form the than molar refractivity value can be calculated by using the Lorentz-Lorentz equation

$$MR = \frac{MW(n^2-1)}{d\ (n^2+2)} \quad (\ cm^3/mol\ )$$

Where mw = molecular wt. N= index of refrection at 20 ^{0C}
d = density at 20 $^{0c.}$

Molecular connectivity indexes are the third type of steric parameter. The degree of branching in given compound is described by molerconncetivity indexes. Connectivity indexes can be calculated by writing Skelton formula without the hydrogen atom.

Insert Formula x X=E (deltai) etc.

Substructure environment, degree of branching, unsaturation is represented bymolecular connectivity.

The steric parameter parachore [P] is defined as molar volume Vwhich has been corrected for force of intermolecular attraction by multiplying with the fourth root of surface tension.

$$[P] = VY^{1/4} = \frac{My^{1/4}}{D}$$ Where M molecular weight D density.

Boiling point and density arenon-additive properties were also correlated with steric feature.

Effect of steric and electronic parameters on lipophilicity: - Due to inductive effect overall lipophilicity[32]is affected and electron withdrawing groups increases Pie value when a hydrogen bonding group is involve. The nitro group and hydroxyl group present at aromatic Skelton , the electron withdrawing inductive effect of the phenyl ring and the nitro group make the non-bonded electrons on the hydroxyl group less available for hydrogen bonding. Theσ and Es is a

function of QSAR activity. Hence compound having substituents with almost the same value of these parameters may be considered as isomeric bioisosters.

EXPERIMENTAL DETERMINATION OF PARTITION COEFICIENT

The partition coefficient [P] is the drug distributionbetween organic phase octanol andaquoes phase water.

$$[P] = \frac{\text{concentration of drug in n -octanol}}{\text{Concentration of drug in water}}$$

The partition coefficient[33] is not independent of concentration and ideally infinite dilution should be used in the study. The lipophilic molecule the low concentration 10^{-5}m below the critical micelle concentration in aquous phase should be used. For prevent the ionisation of drug the 0.1 N Hcl or 0.1 N NaOH may be used.

$$[p] = \frac{[C]\ n - \text{octanol}}{(1-\alpha)\ [C]\ H_2O}$$ where alpha is the degree of ionization.

METHODS USED IN QSAR STUDIES

Shake flask method and random walk model of drug transportation is used in qsar.[34]

Leinear free energy related method used in qsar study. In this approach interaction of drug molecule with biological activity studied with relation to thermodynamic function. It is also called linear free energy (LFE) or extra thermodynamic method. This methods is expressed as

BA = f (ΔL /ΔH, ΔE, ΔEs)depending upon the circumstances this equation can be modified as

log BA = b π + a
= c Pka+a
=dEs+a
= b π+cpka+a
= b π + dEs+a
= b π +cPka+dEs+a

Hansch model and free wilson model are included in liener free energy method.

According to hansch model there are two types of dependent liener and nonliner .

Hansch suggested two processfirstly the journey of drug from the point of entry in the body and secondly drug receptor interaction in the body. Biological activity will be as follows

log BA = a log P + b σ + c Es+d ..... linear

log BA= a log P $\pm$ b (logP)2 ..... non linear

in free wilson model

log BA= contribution of unsubstituted parent compound+ contribution of corresponding substitutents. Free wilson approach is fast, simple, cheap method where no substitution constant like Pi, sigma, Es were considered. If structural is complex than no. of possible substituents will be more at desired positions. Hence the efficiency of this method will be high.

MOLECULAR MODELLING

It is a technique which describe the actual shape, confirmation, size of the molecules which intract with receptors. It is the branch of science that help in designing of drugs with the help of computers and software's. The three dimensionalstructural confirmation analysis to correlate physiochemical paramerts with the biological activity. The softwares used for molecular modeling[35]. aregenrally molecular modeling pro, amber, Hydra, SYBL, FRODO etc. Thesesoftware's are available for calculation of molecular properties for search of new lead compounds.

Toplissdecision tree method help to select a limited no. of substituents which will give good relation between π, σ,and Es. If the biological activity will increases it can be attributed to positive value of π, σ.

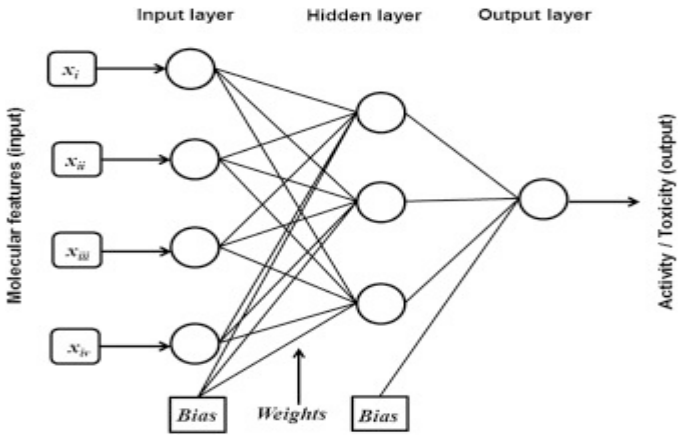
REGRATION ANALYSIS

The multiple linearregreation method (MLR) [36] is used to determine the biological active molecule from the large data pool. MLR is the method used to predict the relationship between two of more explanatory variables by creating a linear equation. Inqsar correlation coefficient r is calculated with the help of graph. Ploting a graph is prefer method to obtained biological activity. The term correlation coefficientr , number of compound utilised n, standard deviation S, and statical validity F is calculated in this method. A regression equation is derived to obtain high value of regressioncoefficient r which indicate the significant of regreation analysis while low value of regreation analysis r

indicate the substituent constant is not important. For a better correlation large no of compound must be used. The value of r must be related to n number of compound for example if r = 0.87 for n=10 is better correlation with r = 0.98 and n=3.
The value of statndard deviation S is large means larger is the accuracy with which the expected activity of new compound can be judge.
The term regreation parameter r^2value help us to understand whether other parameters should be remain counted or uncounted. Greater the value of r^2 lesser the value of variance data that remains unaccounted by the equation.
The term F evaluate in qsar for the statical validity of a particular equation.

QSPR IN DRUG DESIGN
Quantative structure property relationship[37] used in drug design.
The term absortion, distribution, metabolism and elimination is used in pharmacodynamics and pharmacokinetics. The knowledge of rate constant is essential for calculation of dose and dose intervals, estimation of bioavailability and prediction of toxic effect of drug. Pharmacokineticsbehaviour of drugs depends upon QSPR parameters these parameters are absorption rate constants Ka, metabolism rate constant Km, elimination rate constant Kel, volume of distributionVd and degree of plasma protein binding Ka .

ANN (ARTIFICIAL NEURAL NETWORK)
ANNhave been used widely for designing of qsar model between a set of molecular descriptor obtained from the MLR and observed activity.[38] ANN is a good method in qsar to solve the problums arising in pharmaceutical process and product developments.



PURPOSE OF QSAR
QSAR techniques gives hints about the activity of molecules so it save the time and coast of synthesis of chemical molecule. It saves time and effort in clinical trials. It provides the information about the biological activity of the molecules from the large data of molecules so it save time and coast of synthetic chemist.

APPLICATION OF QSAR
QSAR help to know the biological active compounds in a series of molecules. It also gives idea about the toxic substances. It also for cast the biological activity of molecules. It also provides idea about pharmacological response of the molecule in better way. It can be also used to know the surface active agents, purfume, dye and fine chemicals. QSAR provides idea about selection of proper substituents. It is also provide idea about drug receptor interaction. It also provide idea about correlation between various type of parameters and pharmacokinetics feature of drug.

QSAR STEPS
Structural Entry and molecular modelling

Descriptor Generation

CONCLUSION

QSAR is basically used to determine the biological activity of drug but now a day's 3D qsar is very important to correlate the structure feature with the biological activity and its toxic effect if any.

Various newly parameters are used and values calculated with the help of different qsarsoftware'are important to calculate biological activity. Now a day's 4D qsar, 5D qsar, 6D qsar are used but 3D qsar is the base of all model for researcher. Various parameters like electronic, steric etc are used to search the most potent drugs for disease. The role of use of physicochemical parameters is not limited because hydrophobic parameters, electronic parameters, and steric parameters are very important and base of to calculate newly parameters.

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