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# Steric Influence on Anti-Cancer Activity of Phenyl Acridine Derivatives

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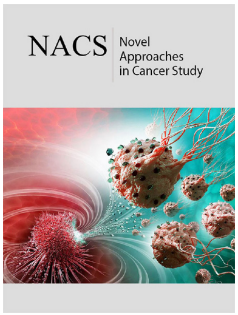


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## Abstract

Present study represents the steric influence on the anti-cancer activity (DNA binding affinity) for the set of 27 Phenyl acridine derivatives. Quantitative structure activity methodology has been adopted to understand the steric influence on the DNA binding affinity of the compounds. Preliminary step of the method is the generation of structural, topological and physicochemical parameters. Relationship between these structural features and DNA binding affinity (logK) has been developed using multiple linear regression analysis.From the study it is observed that the parameters representing steric and volumetric parameters of the molecule are playing dominating role over the other parameters in characterization of the DNA binding of phenyl acridine derivatives as an anti-canceragent. Statistical analysis exhibits the dominance of approximate surface area and surface tension with hydrophobicity and polarizability factors in modeling of DNA binding affinity. QSAR models developed in present study are cross validated by variety of cross validation parameters. The model obtained in the study is useful to model a novel derivative in the series of Phenyl acridines.

## Introduction

Acridine, (with the molecular formula $C_{13}H_9N$), a heterocyclic ring compound seen in crude anthracene. It was separated by treatment and shaking out with dilute sulphuric acid, and then precipitate out the sulphuric acid solution by the treatment of potassium dichromate, the resulting Acridine dichromate being rotten by ammonia [1]. Acridine and its homologues are very stable compounds of weakly basic character. These Acridine analogs can be crystallizes in needles which melt at 110° C and can be characterized or identify by its exasperating action on the skin, and by the blue fluorescence exhibits by the solutions of its salts [2,3]. Phenyl-acridine is the base of chrysaniline, which is the main constituent of the dyestuff phosphine (it is a by-product from the manufacturing of rosaniline) [4].

In addition to the chemical application acridines in the form of Phenyl Acridine exhibits wide spectrum of biological applications, important among these is its anti-cancer biological application. As it is well known fact that protein–DNA interactions shape the basis of different molecular biological processes required for the functioning of cells [5-7]. This form the basis of studies for the scientists to study the DNA-small molecule interactions, for example, interaction of DNA with different types of organic molecules [8-12], inorganic complexes [13-18], fluorescent materials [19,20] and different ions [21-23].

These studies are very helpful to understand the molecular basis of complex diseases and provide help to develop important drug candidates [24]. Most Acridine derivatives interact with DNA as inter-calator. Some bis-acridines bind to DNA through intercalation between consecutive nucleotides [25-27]. Binding of Acridine molecules interferes in the DNA function by blocking the DNA starter which is required by polymerases to synthesize RNA and DNA. In some of the cases the chemotherapeutic action of these Acridine is not restricted to DNA binding, even they also wield their effects on the inhibition of key enzymes such as topoisomerase, telomerase or polymerases. All these interactions are mostly non-covalent in the nature [27-29].

However, there are no reports on the biological activity of 9-phenyl acridine (PAc), although a number of synthetic derivatives of 9-arylacridine are known [30]. Molecular modelling

studies show that these groups of drugs can act as inhibitors of topoisomerase and thus have potential to act as anticancer agents [31]. In this regard, the information about the mechanism of molecule DNA interaction is important to know. Some of the study shows their findings from computational modelling studies about the binding of PAc with DNA [32]. These studies are performed using biophysical techniques to establish the binding of the derivative with DNA and substantiated the findings with the help of molecular modelling studies. The Field of Quantitative Structure Activity Relationships (QSAR) is now well established [33] and this work has demonstrated that the biological activity of a set of 27 Phenyl Acridine derivatives acting via the same mode of action can be mathematically related to some simple physicochemical properties or molecular structure parameters [34,35]. These methods have been widely adopted in the pharmaceutical and agrochemical industries. In the present study efforts has been made to obtain an effective structure activity model which describes the structural requisitions within a Phenyl acridines to display its anti-cancer activity with improved efficacy. QSAR analysis to obtain mathematical model has been done using set of 27 Phenyl Acridine derivatives.

## Methodology

In present study, methodology is based on aspect of Quantitative Structure Activity Relationship i.e, to develop mathematical model based on relation:

$$\Phi = f(C)$$

where,

$\Phi$ = Biological property

$C$ = Structural descriptor/ physicochemical properties

$C$ used in present work is topological indices and physicochemical properties.

### 1.1. Biological activity

Biological activity analyzed in the present study is logK (Association constant) for the set of 27 Phenyl Acridine derivatives. The DNA binding activity is usually expressed in terms of association constant (logK) [36].

### 1.2. Topological/structural parameters

Second generation topological parameters Balaban branching index for hetro atoms using polarizability-based matrix and vander waal weighted matrix are used in present study [37].

### 1.3. Physicochemical properties tested in present investigation

The physicochemical properties describe various structural, physical & chemical assets of the compounds viz., size, polarizability, membrane transportation, inter and intra molecular forces vander Waal's volume, weight etc. these physicochemical features plays the dominating role in deciding the biological activity or function of any molecule or chemical systems. Physicochemical parameter viz., Molar refractivity, Molar volume, Parachor, Index of refraction, Density, Polarizability and Surface Tension (ST) [38,39] is tested in present study, since Surface tension is found to play important role in binding affinity, therefore discussed here.

$$ST = (Pc / MV)^4$$

Since ST is inversely proportional to MV, therefore, this is inverse steric effect.

### 1.4. Logarithm of octanol/water partition coefficient (logP)

The Octanol -Water partition coefficient is the ratio of concentration of specific compound in an Octanol/Water mixture.

$$\log P = \frac{Concentration\ of\ a\ compound\ in\ Octanol}{Concentration\ of\ a\ compound\ in\ water}$$

It shows hydrophobic interaction between a drug and a binding site at a receptor. It is used as a predictor of solute-membrane partitioning. All the above physicochemical properties are calculated using Chemsketch5.0 (www.acdlabs.com) while logP is calculated using available computer program.

Non-conventional physicochemical properties like approximate surface area (ASA), is the parameter used for the representation of size of the molecule with steric influence and tentative area covered with the bonding and overlapping of areas within the molecules [40].

### 1.5. Multiple Linear Regression (MLR)

MLR is an extension of simple linear regression by the inclusion of the extra independent variables

Y= ax1 + bx2 + ……. + constant.

The most familiar standard approaches to QSAR41 are based on multiple linear regression (MLR) and partial least squares (PLS) regression [41-43]. In present study linear mathematical models are developed to study Quantitative structure/Property Activity Relationship. Multiple linear regressions is used to develop models. Topological indices and physicochemical properties are used as independent variables to predict biological properties (dependent variable) as a DNA binding affinity log K of Pac derivatives. Bivariate and multivariate regression has been performed for finding out the best regression models. All those models having value of R below 0.50 are considered to be statistically insignificant.

## Result and Discussion

As mentioned earlier in introduction that the study has been carried out on set of 27 Phenyl Acridine derivatives presented in Table 1 along with their DNA binding affinity. The parent or basic structure of the derivatives is presented in Figure 1. The derivatives shown in Table 1 are studied to explore the role of various structural and physicochemical properties, in DNA binding affinity of PAc. The descriptor which are involved in the QSAR model as a result of MLR

analysis is depicted in Table 2 the QSAR model(s) obtained is shown as Eq 1-4 the best model can be utilize to design new derivative in a series, with more efficacy.

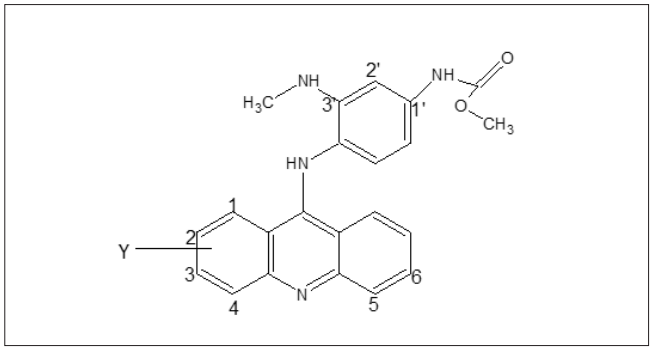


**Figure 1:** Basic structure of Phenyl Acridine derivatives.

**Table 1:** Substituents of Figure 1, Experimental log K, predicted log K of PAc derivatives and residual of Experimental and predicted lof K.

| No. | Substituents (Y) | log K (Obs.) | logK (Calc.) | Residue |
|---|---|---|---|---|
| 1 | H | 6.35 | 5.72 | 0.63 |
| 2 | 2-Me | 5.62 | 6.34 | -0.72 |
| 3 | 3-F | 5.77 | 5.99 | -0.22 |
| 4 | 3-Cl | 6.13 | 6.15 | -0.02 |
| 5 | 3-Br | 6.87 | 5.97 | 0.90 |
| 6 | 3-I | 6.12 | 5.50 | 0.62 |
| 7 | 3-Me | 6.72 | 6.20 | 0.52 |
| 8 | 3-OMe | 6.74 | 6.27 | 0.47 |
| 9 | 3-NO2 | 6.58 | 7.19 | -0.61 |
| 10 | 4-F | 5.82 | 5.98 | -0.16 |
| 11 | 4-Cl | 6.30 | 6.15 | 0.15 |
| 12 | 4-Me | 6.74 | 6.44 | 0.30 |
| 13 | 4-OMe | 6.57 | 6.59 | -0.02 |
| 14 | 4-CONH2 | 6.00 | 6.20 | -0.20 |
| 15 | 4-CONHMe | 6.48 | 6.79 | -0.31 |
| 16 | 3-F,5-Me | 7.37 | 6.57 | 0.80 |
| 17 | 3-Cl,5-Me” | 7.52 | 6.72 | 0.80 |
| 18 | 3-Br,5-Me | 7.52 | 6.62 | 0.90 |
| 19 | 3,5-di-Me | 7.69 | 6.85 | 0.84 |
| 20 | 3-F,5-OMe | 6.27 | 6.83 | -0.56 |
| 21 | 3-Cl,5-OMe | 6.93 | 6.97 | -0.04 |
| 22 | 3-Br,5-OMe | 6.43 | 6.74 | -0.31 |
| 23 | 3-Me,5-OMe | 7.34 | 6.97 | 0.36 |
| 24 | 4,5-di-Me | 7.34 | 6.77 | 0.57 |
| 25 | 4,5-di-OMe | 7.37 | 7.17 | 0.20 |
| 26 | 4-Me,5-CONHMe | 7.12 | 7.42 | -0.30 |
| 27 | 4-OMe,5-CONHMe | 6.95 | 7.71 | -0.76 |

**Table 2:** Structural physicochemical, hydrophobic parameters tested in present study.

| Comp. No. | ST | logP | $J_{HETV}$ | $J_{HETP}$ | ASA |
|---|---|---|---|---|---|
| 1 | 59.4 | 1.19 | 2.140 | 2.136 | 314.35 |
| 2 | 56.7 | 1.34 | 2.150 | 2.146 | 358.46 |
| 3 | 57.7 | 0.59 | 2.157 | 2.150 | 329.00 |
| 4 | 60.4 | 0.97 | 2.171 | 2.145 | 354.04 |
| 5 | 61.5 | 1.24 | 2.180 | 2.142 | 362.95 |
| 6 | 64.7 | 1.70 | 2.183 | 2.136 | 375.44 |
| 7 | 56.7 | 1.34 | 2.140 | 2.136 | 351.17 |
| 8 | 56.0 | 0.19 | 2.137 | 2.133 | 368.16 |
| 9 | 68.4 | -2.98 | 2.157 | 2.153 | 366.58 |
| 10 | 57.7 | 0.71 | 2.187 | 2.18 | 314.32 |
| 11 | 60.4 | 1.09 | 2.202 | 2.175 | 337.64 |
| 12 | 56.7 | 1.47 | 2.169 | 2.165 | 385.92 |
| 13 | 56.0 | 0.32 | 2.190 | 2.185 | 407.64 |
| 14 | 68.0 | -0.17 | 2.186 | 2.182 | 330.89 |
| 15 | 59.8 | 0.08 | 2.164 | 2.160 | 382.3 |
| 16 | 55.2 | 0.74 | 2.188 | 2.182 | 352.71 |
| 17 | 57.7 | 1.12 | 2.202 | 2.177 | 377.81 |
| 18 | 58.7 | 1.39 | 2.211 | 2.175 | 400.41 |
| 19 | 54.4 | 1.49 | 2.172 | 2.168 | 398.88 |
| 20 | 54.5 | -0.41 | 2.212 | 2.205 | 409.52 |
| 21 | 57.0 | -0.03 | 2.225 | 2.201 | 409.12 |
| 22 | 58.0 | 0.25 | 2.233 | 2.198 | 409.12 |
| 23 | 53.8 | 0.35 | 2.196 | 2.192 | 406.38 |
| 24 | 54.4 | 1.62 | 2.201 | 2.197 | 365.01 |
| 25 | 53.2 | -0.67 | 2.249 | 2.245 | 387.2 |
| 26 | 57.4 | 0.23 | 2.203 | 2.199 | 419.94 |
| 27 | 56.8 | -0.91 | 2.234 | 2.229 | 425.93 |

ST= Surface Tension; logP= Octanol /Water partition coefficient; JHETV= Balaban index for hetro atoms with vander wall weighted matrix; JHETP= Balaban index for hetro atoms with polarizability weighted matrix, ASA= Approximate Surface Area

However, Eq 5 is isoparametric to Eq 4 but with 26 derivatives, one derivative is considered as outlier out of 27 and hence excluded from the study being an exceptional derivative and Eq 5 has been developed with 26 PAc derivatives. In present study step up MLR method has been adopted in which mathematical model generation starts from univariate to bi, tri so on and so forth.

logK = 0.0089(±0.0032) ASA – 0.0418 (±0.0258) ST + 5.8021 Eq (1)

n = 27; Se = 0.4781; R = 0.6217; F = 7.562; Q = 1.300

logK = 0.0086(±0.0031) ASA – 0.0484 (±0.0257) ST + 3.2314(±2.268) $J_{HETV}$+ 0.5786 Eq (2)

n = 27; Se = 0.4781; R = 0.6605; F = 5.934; Q = 1.381

logK = 0.0087(±0.0031) ASA – 0.0494 (±0.0257) ST + 3.3948(±1.9566) $J_{HETP}$ +0.5786 Eq (3)

n = 27; Se = 0.4592; R = 0.6764; F = 6.467; Q = 1.381

logK = 0.0056(±0.0035) ASA–0.0857(±0.0328) ST+7.5821(±3.1644) $J_{HETP}$ - 0.2628 (±0.1594) logP - 3.0732 Eq (4)

n = 27; Se = 0.4430; R = 0.7192; F = 5.892; Q = 1.623

logK = 0.0046(±0.0030) ASA–0.0944 (±0.0280) ST+8.2642(±2.6997) $J_{HETP}$ -0.2623 (±0.1355) logP - 3.2910 Eq (5)

n = 26; Se = 0.3766; R = 0.7846; F = 8.408; Q = 2.083

The magnitude of coefficients given in Eq(s) shows relative contribution of the corresponding parameter towards log K. in light of this fact the descending order of the influence of descriptors participating in final mathematical model Eq(5) is - $J_{HEPT}$ > log P > ST > ASA. $J_{HEPT}$ pertaining to the Balaban-type index from polarizability weighted distance matrix represent the polarizability distribution within the molecule, and positive coefficient of $J_{HEPT}$ in Eq 5 represent higher value of this parameter increases binding affinity of PAc derivative with DNA, which results in the formations of stable DNA-PAc derivative complex.

On contrary the negative coefficient of hydrophobic parameter log P represents the negative impact of hydrophobic contours on the binding affinity of the compounds towards DNA. Surface tension is also an important parameter in the Eq (5), which reflects tendency to shrink into the minimum surface area possible. Its negative coefficient indicates that PAc derivatives which undergoes least reduction in its volume during conformational changes, rotational, vibrational or translational motion are effective derivatives. Fourth parameter is approximate surface area of the compound which reflect the overall influential surface area of the molecule or an effective proximate area of the molecule, the positive coefficient of ASA indicate larger the influential area greater will be the DNA binding affinity of the molecule. Eq (5) is considered as a best mathematical model for the theoretical estimation of DNA binding affinity therefore log K of al 26 PAc derivatives has been estimated and presented with their residual values in Table 1,and represented graphically in Figure 2.

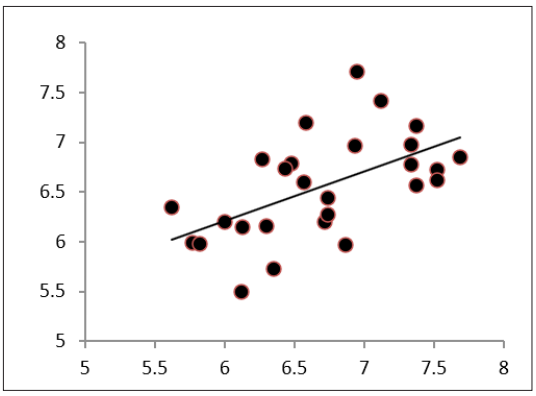


**Figure 2:** Graphical representation of correlation between observed and calculated logK.

## Conclusion

The QSAR analysis performed on the set of 27 Phenyl Acridine derivatives subsequently leads to the conclusion that larger polarized area, lower hydrophobic contour, lesser surface tension and larger approximate surface area is favorable for the DNA binding affinity. The derivative best fitted in these four constrains will exhibits effective DNA binding and subsequently effective anti-cancer agent.

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