Three Dimensional Characters in Drug Receptor Interaction: Study on DNA Binding Affinity with Phenyl Acridine Derivatives

Mamta Thakur, Suprajnya Thakur, and Abhilash Thakur

***Abstract*---** Present study aims to understand the role of 3 Dimensional characters in drug receptor interaction phenomenon of phenyl acridine derivatives in reference to DNA binding affinity for the set of 19 Phenyl acridine derivatives.
The parameters like electronic environment on particular atom, energies and various dimensional aspects at atomic level have to be considered to analyze the 3D characters and its biological response. These parameters are calculated applying Huckel Molecular Orbital Theory with the help of computer software molecular modeling pro.

***Keywords*---** Total energy, Binding energy, Dimensional parameters, DNA binding.

I. INTRODUCTION

DNA is considered as a fascinating target for the treatment of cancer and development of related anticancer drugs. The Intercalator are the most imperative group of compounds that link up with the DNA by having knack to associate with DNA by performing intercalation phenomenon, hence metabolic processes will be hampered. The compounds with intercalating attributes, having common structural features viz, planar polyaromatic systems bind by inclusion between DNA base-pairs. The acridines having planer and pol aromatic structures, imply the molecules to truss DNA with intercalation phenomenon and inhibits the Topoisomerase enzyme. The inhibition of Topoisomerase enzyme check all subsequent steps in the catalytic cycle will eventually cause for the cell death.[1]
The anthracyclines also have a long history in the treatment of cancer. Doxorubicin (adriamycin) and daunomycin were isolated in the 1960s from Streptomycetes. Almost 50 years after their discovery, they are still amongst the most widely prescribed and effective anticancer drugs. The clinical formulations, administration schedules and drug combinations have often changed but the active principle remains the same.[2]

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Thus there has been increase in the interest to words development of compounds with optimal activity for DNA-binding, this may be expected to be used either in place of or in conjunction with, present clinically used compounds.
The interest in the application of virtual tools for the structural analysis in respect to spatial arrangement of molecule has been increasing and highly useful in development of understanding towards the role of three dimensional characters in drug receptor interaction for DNA-binding affinity.

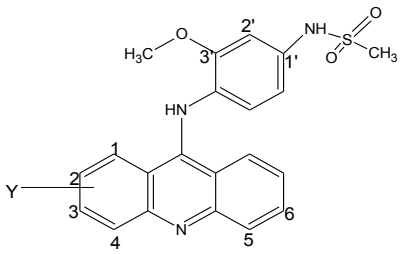

Fig. 1 Parent structure for the Phenyl Acridine derivatives studied in present investigation.

For decades, a number of acridine derivatives have been discovered with potent biological activities, however, due to toxicity and other adverse side effects, most of them were not developed as therapeutic agents. Nevertheless, more recently various chemical modifications of these known active compounds have been carried out to enhance and modify their activity profiles and decrease toxicity.[3]
Number of acridine-based drugs have been successfully utilized as chemotherapeutic agents, such as pyrizaloacridines, imidazoacridinones, anthrapyrazoles, acridinecarboxamides and trizoloacridinones .[4]
Since the intention of this study is to emphasize associations between the biological activity and three dimensional characters of the bio active chemical entity, we shall endeavor to find three dimensional features such as quantum energy parameters and dimensional properties explore the spatial arrangement of the compounds along with electronic features which relate these molecules with their biological activity.

II. METHODOLOGY

In present study methodology adopted is based on aspect of quantitative relationship between quantum energy parameters, electronic environment and dimensional features for the

molecule and their biological activity. To calculate all these quantum molecular properties like energies, electronic parameters and dimensional characters Huckel molecular orbital theory is applied and for the purpose computer software molecular modeling pro is used.

Biological activity, 3D parameters or quantum properties and method of inter relationship analysis is described as below.

Biological Activity:-

Activity analyzed in the present study is the DNA Binding affinity represented as logK. Biological activity logK is adopted from the literature.[5]

A. Electron density[6]

Electron density is the measure of the probability of an electron being present at a specific location. In molecules, regions of electron density are usually found around the atom, and its bonds. In de-localized or conjugated systems, such as phenol, benzene and compounds such as hemoglobin and chlorophyll, the electron density covers an entire region, i.e., in benzene they are found above and below the planar ring.[6]

In compounds with multiple ring systems which are interconnected, this is no longer accurate, so alternating single and double bonds are used.

Electron densities are sometimes probed with X-ray diffraction scans, where X-rays of a suitable wavelength are targeted towards a sample and measurements are made over time to represent, probabilistically, where electrons can be found.[6]

B. Net Charge[7]

Net charge on the atom in molecule is the effect of delocalization of electron density due to the presence or connectivity of atom or group of atoms.[7]

Charge on atom appears due to the presence of electrons and protons in an atom. In a saturated molecule or atom, atoms having the same number of electrons and protons thus the overall charge on an atom should be zero. Due to the presence of surrounding atoms or connectivity with different group of atoms delocalization of electron density may appear to a particular atom, this delocalization of electron density creates the partial charge on particular atom and that may consider as net charge on atom. The delocalization of electron density or net charge on atoms, characterize the specific activity or function for the part of molecule or group of atoms.[7]

C. Total Energy[8]

Total energy is the measure of force in the molecule in form of various bonds present and the non bonding interactions. It is the parameter useful to compare the various conformers of a molecule to study the molecule or analysis for different purposes. In terms of macro molecule or complexes it is the representation of stability in specific environment.[8]

Total energy of the molecule

$$E_{tot} = E_{el} + \sum_{A \neq B} Z_A Z_B / R_{AB}$$

E_{el} - total electronic energy of the molecule
Z_A, Z_B - nuclear charges of atoms A and B
R_{AB} - distance between nuclei A and B

D. Binding Energy[9]

In general, binding energy represents the mechanical work which must be done against the forces which hold an object together, disassembling the object into component parts the energy released/consumed while assembling of various components take place to form any system. At the level of molecule it is the measure of energies incorporated in form of intra molecular bonding amongst the atoms or the energy level for the formation of complex between any two chemical or one chemical and one biological system.[9]

These electronic parameters are calculated using computer software Hyperchem7.[10]

E. Directional or Dimensional Parameters

Directional/Dimensional parameters used in the present investigation are the X, Y and Z coordinates of various atoms in ligand. These X, Y and Z coordinates represents the spatial occupancy of energy field in different directions or dimensions by the specific atoms or electronic arrangements.

F. Regression Analysis[11]:-

In proposed study linear mathematical models will developed to study Quantitative structure/Property Activity Relationship. Multiple linear regressions will be used to develop these models.

Univariate, bivariate to multivariate regression will be performed for finding out the best correlation. All those correlation having value of R below 0.50 will be considered to be insignificant.

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

$$Y = ax_1 + bx_2 + \ldots\ldots + \text{constant}.$$

Goodness of fit of the equation to the data can be obtained by calculation of a multiple correlation coefficient (r^2) just as for simple linear regression.[11]

TABLE I
BINDING OF 1'-$NHSO_2Me$, 3'-OME, 3,5-Y-IV TO POLY[D(G-C)]DNA.

No	Substituents	logK(Obs.)
1	H	5.65
2	3-NH_2	6.13
3	3-NO_2	6.13
4	3-Me	6.08
5	3-OMe	5.97
6	3-Cl	5.98
7	5-$CONH_2$	6.13
8	5-CONHMe	6.18
9	5-$CONHCH_2CONH_2$	6.40
10	3-NH_2,5-CONHMe	6.82
11	3-NO_2,5-CONHMe	6.40
12	3-NO_2,5-CONHMe	6.65
13	3-Me,5-$CONH_2$	6.30
14	3-Me,5-CONHMe	6.68
15	3-Me,5-$CONHCH_2CONH_2$	6.69
16	3-OMe,5-CONHMe	6.82
17	3-Cl,5-$CONH_2$	6.58
18	3-Cl,5-CONHMe	6.65
19	3-Cl,5-$CONHCH_2CONH_2$	6.83

III. Result And Discussion

On the basis of correlation and regression analysis and the result obtained from the study it is observed that the 3D parameters like Energies and dimensional features leading the drug receptor interaction in respect to DNA binding affinity for the Phenyl Acridine derivatives. The primary information explored from the study is the role of three dimensional characters and dimensional parameters in drug receptor interaction phenomenon. In continuation to this bi-parametric and tri-parametric combinations for the set of 19 compounds are tested and the results are presented with the higher value of r are in form of mathematical equations.

Table II
Three dimensional and Quantum parameters used in present investigation.

Com. No.	TE	BE	NCC3	EDC3
1	1273.54	1513.39	0.0376	3.9624
2	1352.23	1603.79	0.2397	3.7603
3	1488.79	1775.24	0.1674	3.8326
4	1350.58	1597.87	0.1132	3.8868
5	1433.57	1698.92	0.3038	3.6961
6	1344.20	1599.45	0.1836	3.8164
7	1497.08	1772.88	0.0377	3.9623
8	1577.83	1861.08	0.3960	3.9604
9	1785.46	2104.67	0.3750	3.9625
10	1662.78	1957.75	0.2434	3.7566
11	1814.12	2143.97	0.1677	3.8323
12	1730.63	2053.04	0.1696	3.8304
13	1578.22	1861.47	0.1135	3.8865
14	1659.22	1949.91	0.1141	3.8859
15	1873.34	2200.00	0.1132	3.8868
16	1751.89	2060.67	0.3049	3.6951
17	1575.37	1866.58	0.1626	3.8374
18	1654.16	1952.81	0.1841	3.8159
19	1866.63	2201.25	0.1798	3.8202

*TE = Total Energy, BE = Binding Energy
NCC3 = Net charge on Carbon 3, EDC3 = Electron Density on Carbon 3.

The models obtained from bi-parametric combinations are given below.

$$\log K = 0.0016(\pm 0.0002033)\ TE + 1.0895(\pm 0.4560)\ NCC3 + 3.7041 \quad (1)$$

n=19, Se=0.1603, R=0.8991, R^2_A =0.7844, F=33.747,Q=5.60

$$\log K = 0.0016(\pm 0.0002033)\ TE - 1.0894(\pm .4560)\ EDC3 + 8.0619 \quad (2)$$

n=19, Se=0.1603, R=0.8991, R^2_A =0.7844, F=33.747,Q=5.60

The statistics generated from study explores that the higher total energy favors the DNA binding affinity. The similar magnitude of total energy in both the equations 1 and 2 shows the linear relationship between total energy and DNA binding affinity. The confirmers having the higher energy lead the drug receptor interaction in reference to DNA binding affinity. It is also observed from the equations that the higher net charge on carbon present at 3rd position tends the molecule toward higher DNA binding affinity at the very same time same carbon atom with high electron density reduces the DNA binding affinity. This may lead the drug receptor interaction indirectly with permeability properties and inductive role. Comparison of contributive magnitudes of the parameters in both equations explore the fact that net charge on Carbon present at 3rd position and electron density on same atom having the similar but apposite magnitude for DNA binding affinity.

Study demonstrates the dominance of energy features over electronic environment at atomic level for DNA binding affinity of studied phenyl acridine derivatives. Extension of bi-parametric equations in to the tri-parametric equation has been done for the further analysis about the role of three dimensional characters in drug receptor interaction specifically for DNA binding affinity of Phenyl acridine derivatives. The tri-parametric models obtained are as below.

$$\log K = 0.0149(\pm 0.0069)\ TE + 1.1598(\pm 0.4231)\ NCC3 - 30.0115(\pm 0.0060)\ BE + 4.226 \quad (3)$$

n=19, Se=0.1482, R=0.9200, R^2_A =0.8158, F=27.566, Q=6.20

$$\log K = 0.0149(\pm 0.0069)\ TE - 1.1598(\pm 0.4231)\ EDC3 - 30.0115(\pm 0.0060)\ BE + 8.8655 \quad (4)$$

n=19, Se=0.1482, R=0.9200, R^2_A =0.8158, F=27.566, Q=6.20

Addition of Binding energy in by parametric equation leads the study towards the domination of energy parameters in drug receptor interactions. It is also observed that there is marginal decrease in the magnitude of parameter total energy and slight increase in the magnitude of electronic parameters but the overall regression value of the models are increased significantly. Increase in the magnitude of electronic parameter indicates that, binding energy govern by the atomic electronic environment in the molecule. Study also revels, higher binding energy may not favor the DNA binding affinity and leads towards the receptor drug complex with moderate energy.

With the same statistics both eq. 3 and 4 shows the similar behavior of binding energy in combination to NCC3 and EDC3. Addition of BE also not affect the linearity of the models.

Calculated value of DNA binding affinity logK from eq. 3 and 4 are presented in Table 4 and graphical representation of correlation is made in figure 2.

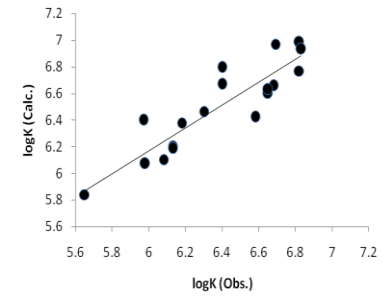

Fig. 2 Graph obtained between observed and calculated logK from eq. 3 and 4.

The information generated from the above equations extended the study towards the dimensional analysis of the phenyl acridine derivatives. For the purpose X, Y and Z coordinates are calculated for carbon atom at 3rd position in the studied compound and correlate with the DNA binding affinity.

TABLE III
DIRECTIONAL OR DIMENSIONAL PARAMETERS USED IN PRESENT INVESTIGATION.

Comp.No.	XC3	YC3	ZC3
1	2.5092	-5.0954	0.0433
2	2.5874	-4.7003	0.0763
3	2.6599	-4.3588	0.0415
4	2.5861	-4.7020	0.0172
5	2.4686	-4.9321	-0.0171
6	2.5792	-4.8040	0.0269
7	2.7077	-4.6071	0.1575
8	3.0618	-4.0961	0.1546
9	4.2020	-3.0854	0.0921
10	2.9835	-3.9789	0.2676
11	2.9719	-3.8372	0.0900
12	2.6650	-4.2865	0.0130
13	2.7207	-4.3880	0.2643
14	3.0061	-3.8103	0.2331
15	4.1691	-2.9041	0.1624
16	2.7419	-3.8778	0.0750
17	2.6927	-4.4981	0.2045
18	3.0829	-3.9816	0.1023
19	4.1655	-2.9438	0.0875

*XC3= Value for X coordinate of Carbon 3.
YC3 = Value for Y coordinate of Carbon 3.
ZC3 = Value for Z coordinate of Carbon 3.

From the perusal of the study it is observed that the any change in direction or dimension from carbon present on 3rd position lead the DNA binding affinity and having significant contribution in drug receptor interaction.

The bi-parametric combination are tested from the 3D parameters and best results obtained from the following combinations.

$$\log K = -0.8089(\pm 0.1792)\, XC3 + 1.0697(\pm 0.1573)\, YC3 + 13.2216 \quad (5)$$

n=19, Se=0.1571, R=0.9033, R^2_A =0.7930, F=35.471, Q=5.70

Equation 5 explores the dominance of directional coordinates of 3rd Carbon in Y dimension over the directional coordinates in other dimensions. It is also revels from the results that the expansion of Carbon atom present at 3rd position, in X or Y dimension may not favor the drug receptor interaction. Expansion of molecule from carbon at 3rd position in X dimension decreases the DNA binding affinity.

It is worthy to mention here that the negative values of Y coordinates for carbon atom on 3rd position in all 19 derivatives indicates that phenyl acridine derivatives are constricted from carbon at 3rd position in Y dimension and model suggests that its expansion in Y dimension may not support to DNA binding affinity.

For further detailed study tri- parametric regression analysis has been performed and the model obtained is as below.

$$\log K = -0.7773(\pm 0.1751)XC3 + 1.0303(\pm 0.1551)\, YC3 + 0.5658(\pm 0.3985)\, ZC3 + 12.9059 \quad (6)$$

n=19, Se=0.1524, R=0.9153, R^2_A=0.8053, F=25.819, Q=6.00

From the perusal of eq. 6 it is exhibited that, the constriction of the molecule at 3rd C in the Y dimension favors the DNA binding but at the very same time expansion in X dimension will not favor the binding phenomenon. Addition of ZC3 in eq.5 is not making the significant difference rather the value of r is increasing. The magnitude of ZC3 is also not exploring the significant role in DNA binding. It helps to maintain the linearity of model and showing the significance of 3rd Carbon in DNA binding Affinity.

Calculated value of logK with eq. 6 is presented in table 4 and graphically in figure 3.

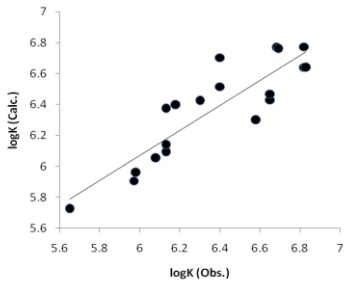

Fig. 3 Graph obtained between observed and calculated logK from eq. 6

TABLE IV
OBSERVED AND CALCULATED VALUES OF DNA BINDING AFFINITY LOGK FROM EQ. 3 AND 6.

Comp.No	$logK^a$	$logK^b$	$logK^c$
1	5.65	5.84	5.73
2	6.13	6.21	6.09
3	6.13	6.19	6.37
4	6.08	6.10	6.05
5	5.97	6.40	5.91
6	5.98	6.07	5.96
7	6.13	6.19	6.14
8	6.18	6.38	6.40
9	6.40	6.67	6.52
10	6.82	6.77	6.64
11	6.40	6.79	6.70
12	6.65	6.60	6.43
13	6.30	6.47	6.42
14	6.68	6.66	6.77
15	6.69	6.97	6.76
16	6.82	6.98	6.77
17	6.58	6.42	6.30
18	6.65	6.63	6.47
19	6.83	6.93	6.64

$logK^a$ = Observed DNA binding affinity taken from the literature[21].
$logK^b$=Calculated DNA binding affinity from eq. 3.
$logK^c$ =Calculated DNA binding affinity from eq. 6

From the perusal of table 2 and 3 it is observed that the expansion of Carbon atom present on 3rd position in X direction and constriction from Y direction help to multiply the total energy of the molecule. Similar relationship demonstrated by the parameters with binding energy of the molecule.

Here also worthy to mention that the higher total energy having the leading role in DNA binding affinity but higher Binding energy is unfavorable for the same but both are highly correlated with the directional parameters in similar fashion. These results indicate about the mutually dependent behavior of the three dimensional characters for drug receptor interaction in respect to DNA binding affinity of studied Phenyl acridine derivatives.

IV. CONCLUSION

On the basis of study carried out it is concluded that the presence of Carbon at 3rd position in Phenyl Acridine derivatives having the significant role in DNA binding affinity. Three dimensional and electronic parameters along with energy parameters can be used significantly to model the drug receptor interaction for the present set of compounds. This also can be concluded that the constriction of the Phenyl Acridine derivatives from 3rd Carbon in the Y dimension is favorable for DNA binding affinity. It is also concluded that the compact spatial arrangement of Phenyl Acridine derivatives requires for drug receptor interaction particularly for DNA binding affinity.

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