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Use of Quantum Chemical Parameters in Biochemical Interaction Analysis of Flavonoid Derivatives as Tyrosin kinase Inhibitors

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Abstract: ***In the present study use of quantum chemical parameters in biochemical interaction analysis is made for the Tyrosin kinase inhibition activity of Flavonoid derivatives. Soft computation methods have been applied to estimate and analysis the quantum chemical parameters for the studied derivatives. Analysis is made on the basis of multiple linear regression analysis and it is observed from the result that the quantum chemical parameters can be used for the prediction of biochemical interaction mechanism and structural or substitution effects on the chemical structure of the molecule lead towards the biochemical behavior of the chemical entity.***

Introduction:

One of the most talented applications of this biological based computer technique is in computer aided molecular design (CAMD). This field has been called many things in different disciplines, but in wide-ranging, it is a design of new molecules based on desired properties. In pharmaceutical development, this efforts is paying attention on modeling the drugs and the biological receptors that the drugs binds to, so that better binding, and therefore, more potent or accurate drugs, can be developed. Evolutionary technique can help achieve the design of totally new molecules, some of that were never even thought of before.

In older times, bioactive molecules have been discovered by one of several methods[1]: exploratory chemical synthesis; screening of natural products; chemical cataloguing of lead compounds; examination of side effects; and serendipity. Although these methods have been, and continue to be, very successful, accounting for the large majority of drugs and agrochemical discovered to date, they are becoming increasingly expensive and time-consuming. As the worth of existing bioactive compounds increases, it becomes more difficult to discover new chemical entities with substantial advantages. The average number of compounds synthesized in order to obtain a profitable candidate has risen from 10,000 to around 40-50,000.

The modern combinatorial methods greatly increase the numbers of compounds synthesized and tested but create very large amounts of data related to the structure of molecule and its biochemical phenomenon. Clearly it has become very important to find new methods for extracting useful molecular design information from these large quantities of structure-activity data.

The continuous development of structural descriptors and statistical equations transformed Quantitative Structure-Activity Relationships (QSAR) and Quantitative Structure- Property Relationships (QSPR) into commanding and widely used models for the prediction of physical, chemical, and biological properties[2-7].

In the present study we have deal with the quantitative structure activity relationship for the set of 19 flavonoid derivatives as tyrosin kinase inhibitors. To understand the biochemical interaction mechanism of inhibition activity of tyrosinkinase we have elucidate the Flavonoid derivatives with the help of computational methods as tool along with the variety of non conventional quantum chemical parameters.

METHODOLOGY:

In proposed study methodology will be adopted is based on aspect of quantitative structure activity relationship. For this purpose various classical physicochemical properties, topological indices and 3D parameters or quantum properties were tested and describe as below,

Biological Activity:-

Activity analyzed in the present study is the log1/C (inverse logarithmic value of 50% Inhibitory Concentration). The Tyrosin Kinase Inhibition activity is usually expressed in terms of inverse logarithmic concentration. In present study this biological activity log1/C is adopted from the literature.[8]

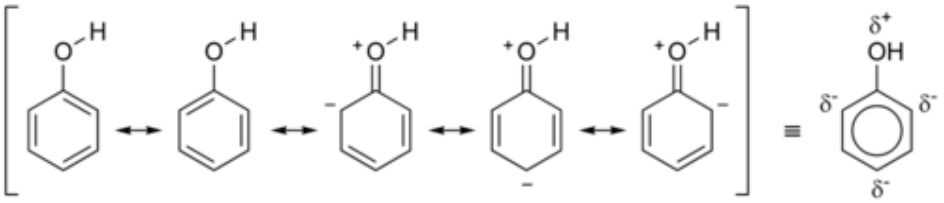
The 3D properties describe various 3D structural/functional features of the compounds viz., Electron density, Net charge, HOMO LUMO etc. these 3D properties may help to characterize membrane transportation, inter and intra molecular forces in Drug receptor complex, Energy of Ligend receptor complex, metabolic function and route of drug transformation, etc. these features plays the dominating role in deciding the biological activity or function of any molecule or chemical systems.

3D properties are proposed to study in the present work is as follows

Electron density

Electron density[9-11] 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. This is sometimes shown diagrammatically as a series of alternating single and double bonds. In the case of phenol and benzene, a circle inside a hexagon shows the de-localized nature of the compound. This is shown below:



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. Quantum electrodynamics and some branches of quantum theory also study and analyze electron superposition and other phenomena with the help of Electron density.

Mulliken population analysis is based on electron densities in molecules and is a way of dividing the density between atoms to give an estimate of atomic charges and prediction of probable active site of the molecule/Atom.

Net Charge

Net charge[9-11] 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.

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.

HOMO and LUMO

HOMO and LUMO[9-11] are acronyms for highest occupied molecular orbital and lowest unoccupied molecular orbital, respectively. The difference of the energies of the HOMO and LUMO, termed the band gap, can sometimes serve as a measure of the excitability of the molecule: the smaller the energy, the more easily it will be excited.

The HOMO level is to organic semiconductors and quantum dots what the valence band is to inorganic semiconductors. The same analogy exists between the LUMO level and the conduction band. The energy difference between the HOMO and LUMO level is regarded as band gap energy.

When the molecule forms a dimer or an aggregate, the proximity of the orbitals of the different molecules induces a splitting of the HOMO and LUMO energy levels. This splitting produces vibrational sublevels which each have their own energy, slightly different from one another. There are as many vibrational sublevels as there are molecules that interact together. When there are enough molecules influencing each other (e.g. in an aggregate), the number of sublevels are large enough to be perceived as a continuum rather than discrete levels.

Total Energy

Total energy[9-11] 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.

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

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

Binding Energy

Binding energy[9-11] represents the mechanical work which must be done against the forces which hold an object together, disassembling the object into component parts separated by sufficient distance that further separation requires negligible additional work or 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.

At the atomic level the atomic binding energy of the atom derives from electromagnetic interaction and is the energy required to disassemble an atom into free electrons and a nucleus.

Electron binding energy is a measure of the energy required to free electrons from their atomic orbits. This is more commonly known as ionisation energy.

At the nuclear level, binding energy is also equivalent to the energy liberated when a nucleus is created from other nucleons or nuclei. This nuclear binding energy (binding energy of nucleons into a nuclide) is derived from the strong nuclear force and is the energy required to disassemble a nucleus into the same number of free unbound neutrons and protons it is composed of, so that the nucleons are far/distant enough from each other so that the strong nuclear force can no longer cause the particles to interact.

In astrophysics, gravitational binding energy of a celestial body is the energy required to expand the material to infinity. This quantity is not to be confused with the gravitational potential energy, which is the energy required to separate two bodies, such as a celestial body and a satellite, to infinite distance, keeping each intact (the latter energy is lower).

These electronic parameters are calculated using computer software ChemSW[12].

Directional or Dimensional Parameters:

Dimensional parameters[9-11] 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.

Regression Analysis:

In the present study linear mathematical models are developed to study biochemical interaction mechanism. Multiple linear regressions[12] is used to develop the models for analysis.

Univariate, bivariate to multivariate regressions are performed for finding out the best correlation and analysis of biochemical interaction aspects. All those correlation having value of R below 0.50 are 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.

Result and Discussion:

In the present study analysis about the use of quantum chemical parameters in the biochemical interaction of tyrosin kinase inhibitors is made. From the aforementioned study we found the set of 19 flavonoid derivatives from the earlier studies with exceptional behavior in respect of their structural response to the receptor. This has been findout with the values of their residues. Theses nineteen compounds are presented in table 1 and parent structure of these derivatives is present in figure 1. (comp. no 1, 3, 4, 5, 6, 7, 8, 9, 11, 13, 14, 21, 22, 39, 45, 52, 53, 87, 93. From the parent series of derivatives) [8]

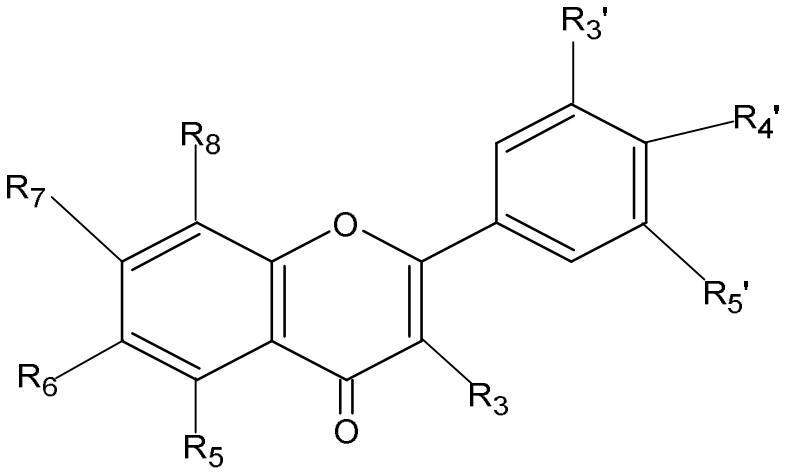


Figure 1. Parent structure of flavonoid derivatives used in present study.

Table1. Structural details of Flavonoid derivatives and their biological activity log1/C.

No.	Parent No.	Substituents	log1/C(Obs.)
1.	1	5,7-OH,4-NH_2	5.13
2.	3	3,7,3,4-OH	4.86
3.	4	5,7,4-OH	4.83
4.	5	5,4-OH	4.80
5.	6	6,3-OH	4.80
6.	7	6-OH,5,7,4-NH_2	4.74
7.	8	5,7-OH	4.71
8.	9	4-OH,3,5-OCH_3	4.57
9.	11	7,3-OH	4.41
10.	13	6-OMe,8,3-NH_2	4.25
11.	14	6-OH,3,4,5-OCH_3	4.22
12.	21	7,4-OH,3,5-OCH_3	3.92
13.	22	6-OH,4-OR	3.92
14.	39	6-OH,3,5-OCH_3,4-OR	3.43
15.	45	7-OH,6,8,4-NH_2	3.12
16.	52	3-COOH,4-OH	2.80
17.	53	5-OMe,8,4-NH_2	2.79
18.	87	3-COOMe,5,7-OBn,4-NO_2	2.70
19.	93	3-COOMe,6-OMe,4-OH	2.70

We tested the topological indices for these compounds in previous chapter thus we test quantum chemical and dimensional parameters for these nineteen compounds in the present study.
This analysis is made for the better utilization of quantum properties in development of more predictive and suitable model and better characterization of the Tyrosin kinase inhibition activity of Flavonoid derivatives.
These quantum and dimensional parameters viz, HOMO, LUMO, Total Energy and Binding Energy are presented in Table 2. The parameters like net charge and electron density on different atom in the molecule are presented in Table 3.
X, Y and Z Coordinates tested in present study are presented in Table 4, 5 and 6 respectively.

Table 2. HOMO, LUMO and energy parameters tested in present study.

S.No.	HOMO	LUMO	TE	BE	
1	-0.152556	-0.112003	1273.54247	1513.385546	
2	-0.155327	-0.1121945	1352.23274	1603.791427	
3	-0.1627	-0.1122968	1488.79354	1775.238691	
4	-0.164544	-0.1123748	1350.58235	1597.867888	
5	-0.161472	-0.1121256	1433.55647	1698.923968	
6	-0.161428	-0.121696	1344.2034	1599.454455	
7	-0.163029	-0.1122168	1497.07952	1772.885164	
8	-0.16968	-0.1123062	1577.8345	1861.082594	
9	-0.142001	-0.111888	1785.46076	2104.671427	
10	-0.174341	-0.1124076	1662.78371	1957.747412	
11	-0.174938	-0.1126748	1814.12388	2143.974054	
12	-0.172314	-0.1127176	1730.62963	2053.037353	
13	-0.160028	-0.1122058	1578.2231	1861.471193	
14	-0.157308	-0.1120886	1659.22002	1949.91057	
15	-0.157956	-0.1119192	1873.3425	2199.995616	
16	-0.153918	-0.1125125	1751.89492	2060.667441	
17	-0.153232	-0.1204153	1575.36741	1866.58103	
18	-0.163013	-0.1221232	1654.1575	1952.813572	
19	-0.158492	-0.1215702	1866.63259	2201.251219	

Highest occupied molecular orbital energy (HOMO), Lowest unoccupied molecular orbital energy (LUMO), TE=total energy, BE=Binding energy

Table 3: Net charge and Electron density on various atoms tested in present study.

S.No.	NCC3	NCC5	NCC9	EDC3	EDC5	EDC9
1	3.76E-02	-5.36E-02	-0.6684	3.96244	4.054	5.66839
2	0.23969	-5.74E-02	-0.6923	3.76031	4.057	5.69232
3	0.16736	-5.16E-02	-0.6633	3.83264	4.052	5.6633
4	0.11317	-5.28E-02	-0.6717	3.88683	4.053	5.67174
5	0.30385	-5.44E-02	-0.6807	3.69615	4.054	5.68074
6	0.1836	-5.17E-02	-0.6537	3.8164	4.052	5.65367
7	3.77E-02	-1.30E-02	-0.6672	3.96233	4.013	5.6672
8	3.96E-02	-1.98E-02	-0.6658	3.96036	4.02	5.66583
9	3.75E-02	-3.02E-02	-0.6623	3.96248	4.03	5.66228
10	0.2434	-2.93E-02	-0.6846	3.7566	4.029	5.68462
11	0.16773	-2.14E-02	-0.662	3.83227	4.021	5.66203
12	0.16962	-0.01785	-0.6586	3.83038	4.018	5.65865
13	0.1135	-1.89E-02	-0.6705	3.8865	4.019	5.67046
14	0.11412	-0.02777	-0.6645	3.88588	4.028	5.66448
15	0.1132	-3.10E-02	-0.6628	3.8868	4.031	5.66281
16	0.30493	-2.74E-02	-0.6755	3.69507	4.027	5.6755
17	0.16258	-1.99E-02	-0.656	3.83742	4.02	5.65602
18	0.18409	-2.38E-02	-0.6527	3.81591	4.024	5.65266
19	0.17976	-2.99E-02	-0.6449	3.82024	4.03	5.64493

NCC3 = net charge of carbon atom at position 3, NCC5 = net charge of carbon at at position 5, NCC9 = net charge of carbon atom at position 9, EDC3 = electron density of carbon atom at position 3, EDC5 = electron density of carbon atom at position 5, EDC9 = electron density of carbon atom at position 9

Table 4: Coordinates for X direction of the Flavonoids derivatives tested in present study

S.No.	XC3	XC5	XC9	
1	2.5092	-3.456202	-1.130901	
2	2.5874	-3.393101	-1.059502	
3	2.6599	-3.338902	-0.990501	
4	2.58605	-3.387249	-1.05975	
5	2.4686	-3.525	-1.178801	
6	2.5792	-3.391602	-1.060602	
7	2.70775	-3.269251	-0.936251	
8	3.06185	-2.93125	-0.58795	
9	4.202	-1.781401	0.5578003	
10	2.98355	-3.016449	-0.665348	
11	2.97195	-3.04435	-0.685249	
12	2.665	-3.339802	-0.985601	
13	2.7207	-3.276901	-0.927801	
14	3.00605	-2.987551	-0.64105	
15	4.1691	-1.813101	0.5256996	
16	2.74195	-3.260849	-0.90925	
17	2.6927	-3.301901	-0.956202	
18	3.08295	-2.914351	-0.567452	
19	4.16555	-1.820852	0.5209484	

XC3=X-coordinate of carbon atom at position 3, XC5=X -coordinate of carbon atom at position 5, XC9=X-coordinate of carbon atom at position 9,

Table 5: Coordinates for Y direction of the Flavonoids derivatives tested in present study

S.No.	YC3	YC5	YC9
1	-5.09545	-4.30155	-4.85045
2	-4.70035	-4.00295	-4.520249
3	-4.3588	-3.850801	-4.295899
4	-4.702051	-3.98345	-4.507851
5	-4.932152	-4.351651	-4.82225
6	-4.804	-4.088699	-4.612199
7	-4.607151	-3.88875	-4.411751
8	-4.096151	-3.48345	-3.965752
9	-3.085451	-2.631851	-3.035051
10	-3.978951	-3.576849	-3.97225
11	-3.837198	-3.4028	-3.8251
12	-4.2865	-3.880599	-4.2888
13	-4.388	-3.8587	-4.306101
14	-3.81035	-3.38335	-3.78195
15	-2.904099	-2.5281	-2.898599
16	-3.87785	-3.481949	-3.88195
17	-4.49815	-3.99085	-4.42585
18	-3.981601	-3.459599	-3.903399
19	-2.943851	-2.567951	-2.934851

YC3=Y-coordinate of carbon atom at position 3
YC5=Y-coordinate of carbon atom at position 5
YC9=Y-coordinate of carbon atom at position 9

Table 6: Coordinates for Z direction of the Flavonoids derivatives tested in present study

S.No.	ZC3	ZC5	ZC9
1	4.33E-02	0.3131001	0.2116001
2	7.63E-02	0.3472002	0.2401001
3	4.15E-02	0.34285	0.23175
4	1.72E-02	0.3324001	0.2163001
5	-1.71E-02	0.34305	0.21825
6	2.69E-02	0.3275	0.2191
7	0.1575	0.2153001	0.2004001
8	0.1545999	9.03E-02	0.1061
9	9.21E-02	8.97E-02	9.14E-02
10	0.2675999	9.47E-02	0.1526999
11	9.00E-02	0.1356001	0.1246001
12	1.30E-02	0.2508001	0.1720002
13	0.2643499	0.33135	0.3181499
14	0.23315	0.29775	0.28385
15	0.1624	0.2204001	0.207
16	7.50E-04	0.1610501	0.1078501
17	0.2045499	0.19835	0.20275
18	0.10235	0.16505	0.14545
19	8.75E-03	0.1427501	0.1006501

ZC3=Z-coordinate of carbon atom at position 3, ZC5=Z -coordinate of carbon atom at position 5
ZC9=Z-coordinate of carbon atom at position 9

From the perusal of uni parametric corrrelation it is observed that the quantum parameters viz Energies and dimensional features dominates the quantum properties in modeling of Tyrosin kinase inhibition activity of flavonoids derivatives but not mentioned as not having the statistically significant value. As we have the primary information about the role of quantum and dimensional parameters in binding phenomenon we have tested 171 bi-parametric combinations for the set of 19 compounds and the results are produced with the higher value of regression are presented in form of mathematical equation.

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

$\log 1/C = 0.0016(\pm 0.0002033)\ TE + 1.0895(\pm 0.4560)\ NCC3 + 3.7041$ (1)
$n=19,\ Se=0.1603,\ R=0.8991,\ R^2_A=0.7844,\ F=33.747,\ Q=5.60$

$\log 1/C = 0.0016(\pm 0.0002033)\ TE - 1.0894(\pm .4560)\ EDC3 + 8.0619$ (2)
$n=19,\ Se=0.1603,\ R=0.8991,\ R^2_A=0.7844,\ F=33.747,\ Q=5.60$

As the statistics generated from eq. 1 and 2 it is observed that, total energy of the compound and the carbon present at 3rd position with higher net charge or lower electron density playing the dominating role in reference to Tyrosin kinase inhibition activity. Comparison of both equations also explore the fact that net charge on C3 and electron density on same atom having the similar but apposite magnitude for Tyrosin kinase inhibition. Comparison of magnitude between TE and NCC3 or EDC3 exhibits the dominance of total energy over these two parameters for Tyrosin kinase inhibition activity of phenyl flavonoids derivatives. The higher magnitude of Total energy in combination with Net charge and electron density directed the relationship towards linearity.

Extension of bi-parametric models has been done for the further analysis of structural and chemical requirements for Tyrosin kinase inhibition activity of flavonoids derivatives. For the purpose 969 tri-parametric combinations are tested and the best models obtained are given below.

log1/C= 0.0149(±0.0069) TE + 1.1598(±0.4231) NCC - 30.0115(±0.0060) BE + 4.226 (3)

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

log1/C= 0.0149(±0.0069) TE - 1.1598(±0.4231) EDC3 - 0.0115(±0.0060) BE + 8.8655 (4)

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

With the combination of binding energy tri-parametric equation are developed, these equations shows that on addition of Binding energy there is no change in the magnitude of parameters but the overall regression value of the models are increased. Eq, also shows that binding energy also plays the negative role in leading Tyrosin kinase inhibition activity. 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.

For the further detailed study 3876 tetra parametric combination are tested but increase in the value of regression or the predictive potential was not adequate to explain the Tyrosin kinase inhibition activity for flavonoids derivatives.

Calculated value of Tyrosin kinase inhibition activity log1/C from eq. 3 and 4 are presented in Table 7 and graphical representation of correlation is made in figure 2.

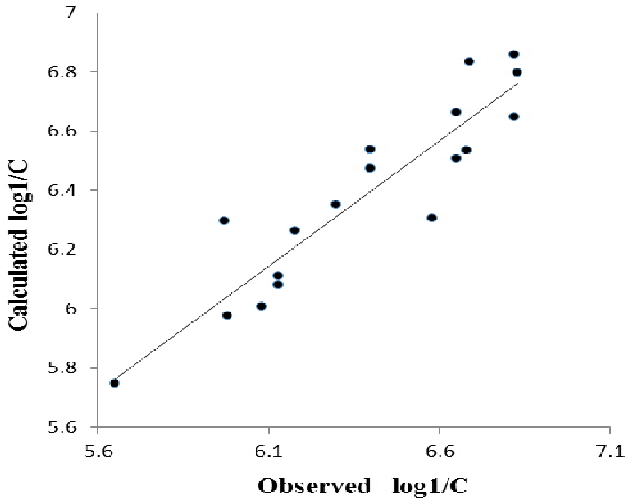


Figure 2: Graph obtained between observed and calculated log1/C from Eq. 12

Table 7. Observed and Calculated values of log1/C from Eq. 3&4.

Comp.No.	log1/C OBS	log1/C CAL	Residuals
comp 1	5.65	5.74	-0.09
comp 2	6.13	6.1	0.03
comp 3	6.13	6.07	0.06
comp 4	6.08	6.02	0.06
comp 5	5.97	6.29	-0.32
comp 6	5.98	5.97	0.01
comp 7	6.13	6.07	0.06
comp 8	6.18	6.26	-0.08
comp 9	6.4	6.53	-0.13
comp 10	6.82	6.64	0.18
comp 11	6.65	6.66	-0.01
comp 12	6.4	6.47	-0.07
comp 13	6.3	6.35	-0.05
comp 14	6.68	6.53	0.15
comp 15	6.69	6.83	-0.14
comp 16	6.82	6.85	-0.03
comp 17	6.58	6.3	0.28
comp 18	6.65	6.5	0.15
comp 19	6.83	6.79	0.04

log1/C OBSERVED=observed value of biological activity taken from literature.
log1/C CALCULATED=calculated value of biological activity obtained by the value suggested by the regression model(equation 3).
RESIDUALS=. It is the difference (or left over) between the observed value of the biological activity and the value suggested by the regression model.
The information generated from the above equations extended by the study towards the dimensional analysis of the flavonoids derivatives. For the purpose X, Y and Z coordinates are calculated for various atoms in the studied compound and correlate with the Tyrosin kinase inhibition activity. Uni-Parametric correlation of directional parameters with Tyrosin kinase inhibition activityalso present in Table 4. From the perusal of Table 4 it is observed that the change of 3rd C in the Y direction or dimension having the significant role in leading the Tyrosin kinase inhibition activity. Similarly the expansion or constriction of 9th Nitrogen in X direction, lead the activity of the molecule.
The bi-parametric combination tested from the 3D parameters and best results obtained from the following combinations.
log1/C=-0.8089(±0.1792) XC3+1.0697(±0.1573) YC3+13.2216 (5)
n=19, Se=0.1571, R=0.9033, R^2_A=0.7930, F=35.471, Q=5.70
log1/C=-0.7734(±0.1703) XC5+1.0365(±0.1497) YC3+8.3452 (6)
n=19, Se=0.1566, R=0.9040, R^2_A=0.7943, F=35.755, Q=5.77
log1/C=-0.7968(±0.1764) XC9+1.0592(±0.1551) YC3+10.2358 (7)
n=19, Se=0.1571, R=0.9033, R^2_A=0.7930, F=35.485, Q=5.74
Eq. 5, 6 & 7 explore the dominance of expansion of 3rd Carbon from Y dimension over the constriction of Carbon 3, 5 and Carbon 9 in X direction. Equations also demonstrate the inverse relationship between the expansion of carbon 3 & 5 in X dimension with. It is also shown by the eq. 16 that the constriction of 9th C in X dimension favors the tyrosin kinase inhibition of flavonoid derivatives.
For further detailed study tri- parametric regression analysis has been performed and the models obtained are given as below
log1/C= -0.7773(±0.1751) XC3+1.0303(±0.1551)YC3+0.5658(±0.3985)ZC3+12.9059 (8)

n=19, Se=0.1524, R=0.9153, R^2_A =0.8053, F=25.819, Q=6.00
log1/C=-0.7430(±0.1667)XC5+0.9983(±0.1477)YC3+0.5613(±0.3976)ZC3+8.2207 (9)
n=19, Se=0.1520, R=0.9158, R^2_A =0.8063, F=25.979, Q=6.02
log1/C=-0.7657(±0.1725)XC9+1.0202(±.1529)YC3+0.5662(±.3984) ZC3 +10.0368 (10)
n=19, Se = 0.1523, R=0.9153, R^2_A =0.8054, F=25.837, Q=6.00

From the perusal of eq.8 it is exhibited that, the expansion of the molecule from 3rd C in the Y dimension favors the Tyrosin kinase inhibition but at the very same time expansion in X dimension will not favor the binding phenomenon. Addition of ZC3 in eq. 14 is not making the significant difference rather the value of r is increasing. The magnitude of ZC3 is also not exploring the dominance in Tyrosin kinase inhibition. It helps to maintain the linearity of model and showing the significance of 3rd Carbon in Tyrosin kinase inhibition activity. As shown from the eq. 18 the expansion of molecule in X direction from 5th Carbon also unfavorable for Tyrosin kinase inhibition. The combination of ZC3 with YC3 and XC3 having the marginal increase in the value of r with the conformation of findings from eq. 5, 6 & 7.

Eq. 10 explores the role of 9th Carbon in Tyrosin kinase inhibition activity. Comparison of all three equations and the magnitude of parameters in equations show that, the expansion of molecule in X dimension will not favor the Tyrosin kinase inhibition activity for flavonoids derivatives.

On the basis of regression result and structural analysis with 2d and quantum parameters modeling studies have been performed using Molecular mechanics technique applying MM+ force field. By the optimization process Total energy, dipole moment and RMS gradient are calculated for the compounds having the minimum residue from Eq. 3 and 4.

Table 9. Modeling parameters calculated for the compounds having the minimum residue.

Compound no.	DpM	RMSg	TE
Comp.no.2	5.27	0.08959	22.47249
Comp no.6	4.126	0.09649	18.88293
Comp no.11	3.605	1.0620	280.3909
Comp.no.16	6.204	0.2823	152.7333
Comp.no.19	6.476	0.5972	22.63967

These calculated modeling properties are correlated with log1/C. The values of all parameters are recorded in Table 9. From the table 9 it is observed that the value of dipole moment is highly rationalized for all the five compound thus it has an important role in Tyrosin kinase inhibition. Very poor correlation has been shown by the RMS gradient and indicates the no linear role of molecular flexibility in Tyrosin kinase inhibition activity. It might play the role as induced function in nonlinear form. Similarly total energy is correlated with binding affinity for the five compounds & showing no direct role in Tyrosin kinase inhibition activity.

Model obtained from DpM is presented in the equation below.

log1/C= 0.1469 (±0.1060) DpM + 4.0404 (11)
n = 5, Se = 0.2665, R = 0.6247, F = 1.920, Q = 2.322

All the five molecules tested in modeling studies are also studied in molecule-molecule (Superimposing) Docking to analysis the distortion in the molecule with substitution. For the same these selected five molecules are superimposed over the parent structure and distance gradient is calculated. Calculated values of distance gradient are presented in Table 10 and superimposed molecules with their energy field are presented in figure 3 to 7.

log1/C = 11.8705 (±6.6636) DG + 6.0780 (12)
n = 5, Se = 0.3218, R = 0.7170, F = 3.173, Q = 2.22

Correlation between the distance gradient and log1/C explore the important role of distortion or distance gradient for Tyrosin kinase inhibition activity. It is worthy to consider the site of distortion and orientation of distortion in the molecule from the parent structure due to substitution or intra molecular forces to understand the role of distortion on Tyrosin kinase inhibition. Thus the result of eq. 12 is analyzed referring to eq. 8, 9 and 10. From the combine analysis of the four equations explored that the distortion should expand the molecule in Y and Z directions from 3rd Carbon and also it should constrict in X direction from 3rd Carbon, 5th Carbon or from the 9th Carbon to favor the Tyrosin kinase inhibition activity.

Table 10. Distance gradient calculated from molecule to molecule superimposing for Phenyl Flavonoids derivatives.

Comp. No.	Distance gradient
Case no.1	1.1961×10^{-2}
Case no.2	2.2423×10^{-2}
Case no.3	2.0334×10^{-2}
Case no.4	4.3579×10^{-2}
Case no.5	7.1876×10^{-2}

Here it is worthy to mention that the Tyrosin kinase inhibition activity represented by log1/C which is actually association constant and higher the value of association constant higher the rate of binding. Thus the Tyrosin kinase inhibition activityis represented with log1/C

Observation of superimposed structures reveals the information about the change in the orientation of Methoxi group attached with phenyl ring on parent molecule. It may due to substitution on fused phenyl rings. It is also observed in the figure 3 that the presence of NH_2 on 3rd position will not change the orientation of methoxi group on phenyl ring but it changes the orientation of methyl sulphonamide group in space attached on the same phenyl ring. From the perusal of figure 4 - 7 it is informed that the presence of electronegative group on 3rd position or di substitution on 3rd and 5th position or any bulky change in substitution on 5th position like 3-(formylamino) propanamide changed the orientation of Methoxi group on phenyl ring along with the change in spatial orientation of the different groups present on the same ring.

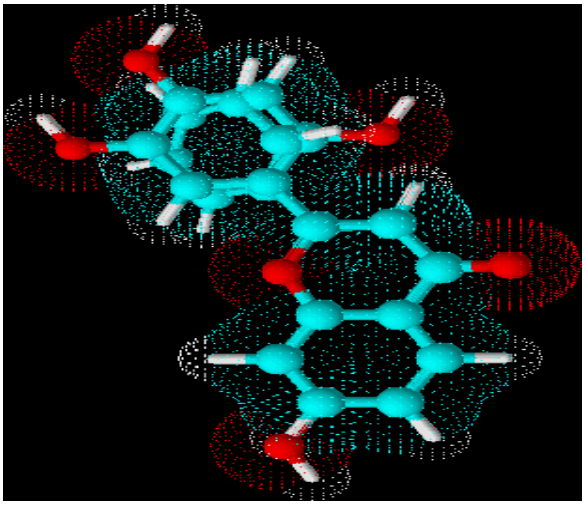


Figure 3. Molecular superimposing of compound 3 on parent molecule.

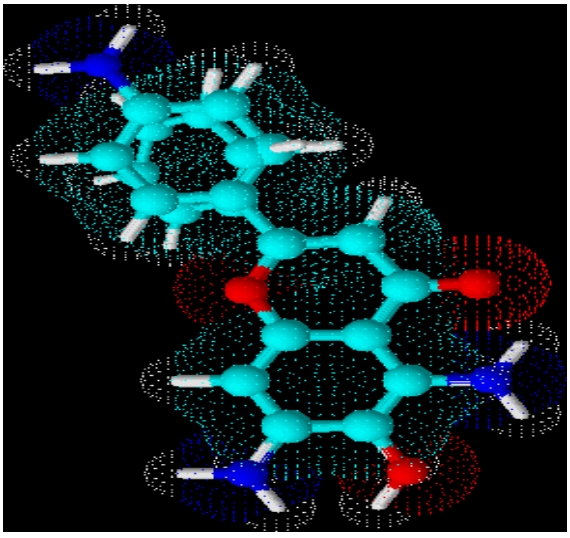


Figure 4. Molecular superimposing of compound no 7 on parent molecule.

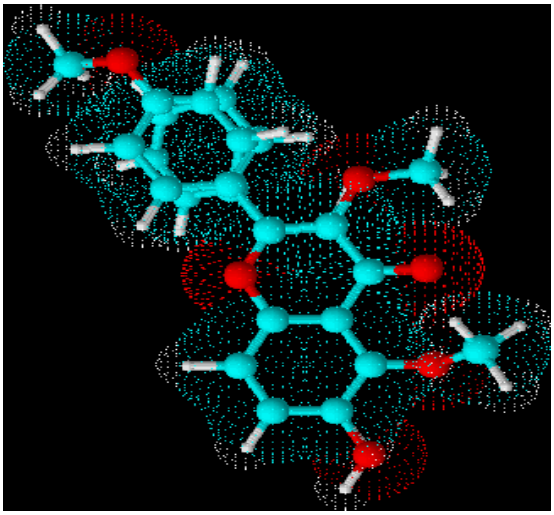


Figure 5. Molecular superimposing of compound no 14 on parent molecule.

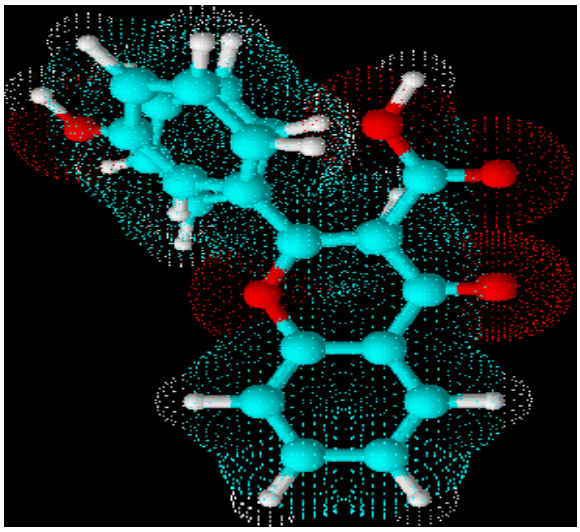


Figure 6. Molecular superimposing of compound no 52 on parent molecule.

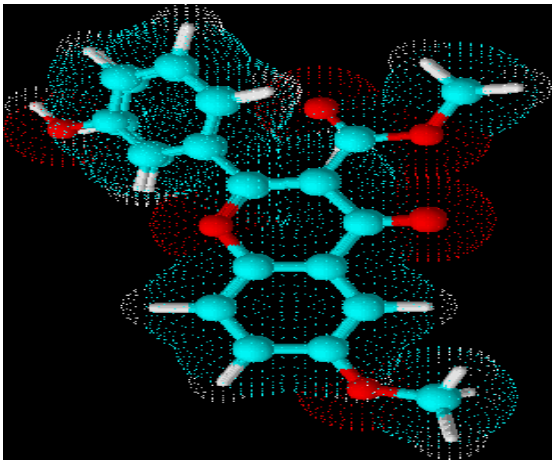


Figure 7. Molecular superimposing of compound no 93 on parent molecule.

Conclusion:

The statistical analyses based on the multipal regression analysis led us to propose the utilization of the quantum chemical parameters covers a wide range of substituents as well as a verity of biochemical interaction involve in the enzyme – inhibitors complex. The models proposed in present work are more useful in describing use of quantum chemical parameters in prediction of p56lck Protein Tyrosin kinase Inhibition from Flavonoid derivatives.

With the analysis conclusion can be drawn that the presence of NO_2 is favorable for the biochemical interaction of the derivatives. Study also explores the fact that the total energy of the compound playing the dominating role in reference to Tyrosin kinase inhibition activity. It also reveals that the carbon present at 3rd position with higher net charge or lower electron density playing the important role in reference to Tyrosin kinase inhibition activity. Expansion of the molecule from 3rd Carbon in Y dimension, lead the studied biological activity. Constriction of 9th C in X dimension favors the tyrosin kinase inhibition for flavonoids derivatives. Dipole Moment playing the important role for the set of five compounds in receptor interaction process, but showing no direct role in Tyrosin kinase inhibition activity. From the superimposition study it can be conclude that the distortion should expand the molecule in Y and Z directions from 3rd Carbon and also it should constrict in X direction from 3rd Carbon, 5th Carbon or from the 9th Carbon to favor the Tyrosin kinase inhibition activity.

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