Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(8):150-156
(http://www.derpharmachemica.com/archive.html)

Computational Chemistry Application of Physicochemical Descriptors: QSAR Study on Some β-Carboline Compounds

Oraas Adnan Hatem*

Department of Chemistry, College of Science, Al-Qadisiyah University, Diwaniay, Iraq

ABSTRACT

In the present investigation, the applicability of various physicochemical parameters has been tested for the QSAR study on some β-carboline compounds extracted from Harmine, in order to predict new unprepared derivatives with the best activity as a potent anticancer agent. Quantitative Structure Activity Relationship (QSAR) has been derived for a set of β-carboline compounds to explore the relationship between the physicochemical properties (such as: heat of formation, partition coefficient, molar refractivity, ΔE HOMO-LUMO, Ionization Potential (IE), Electron Affinity (EA), Chemical Hardness (η), The Electronegativity (χ) and Global electrophilicity Index (ω) and activity expressed as logIC_{50}. Multi-linear Regression Technique (MLR) has been employed and the model gave significant regression coefficients. The physicochemical properties of each compound were obtained utilized GUSSAIN software at the PM3 (Parametric Method 3) level after full geometry optimization. Three new β-carboline compounds have been predicting with an interested very high value of activity, where the value of Log IC_{50} was -18.932, -18.747and -23.66 for N1-βC, N2-βC and N3-βC respectively. The more active β-carbolines are all more lipophilic and larger than the less active compounds.

Keyword: Computational drug design, β-Carboline, QSAR, GUSSAIN, PM3, MLR, Physicochemical properties, Esophageal cancer

INTRODUCTION

Cancers are considered as the major cause of death in the world. It can be defined as an abnormal and uncontrolled cells proliferation that continued even with eradicating of the causing factors. research both in the field of cancer biology to understand the mechanisms behind developing of cancers and also in the field of therapeutic targeting of cancer are developed widely over the last few year, as it is essential to understand the disease in order to treated. Chemotherapies are widely used in cancer therapy. However, in addition to the obvious pro of killing the tumor cells, killing the normal cells is consider one of the major drawback of such therapies [1].

Trying to design and develop anticancer drugs that can target tumor cells and stimulate its apoptosis independently of normal cells are the most important nowadays research focusing. The developing of anticancer drugs with photoactive constituents consider as an essential mechanism to cultivate a less toxic anticancer drugs [2,5].

β-carboline compounds are a family of alkaloids, characterized by indole structure in a core and a pyridine ring, they are one of the important phytoconstituents that can overcome the cancer cells intrinsic resistance to apoptotic stimuli. β-carbolines that are structurally related to harmine, which is isolated from plants, including the Middle Eastern grass harmal or Syrian rue (*Peganum harmala*) and the South American vine ayahuasca (*Banisteriopsis caapi*) [6].

The biochemical mechanisms of these compounds are depending on DNA intercalation and inhibition of Dual-specificity Tyrosine Phosphorylation Regulated Kinase 1A (DYRK1A) an enzyme involved in the uncontrolled cell proliferation and cancer cell chemo-resistance. It is a dual-specificity protein kinase that auto phosphorylates a conserved tyrosine residue in the activation loop but phosphorylates exogenous substrates only at serine or threonine residues. DYRK1A is found to be overexpressed in melanomas intrinsically resistant to apoptotic stimuli [7].

DYRK1A inhibition was suggested to activate the apoptotic enzyme, caspase-9, which leads to massive apoptosis in some of the most poor prognosis cancers such as glioma, esophageal cancer and non-small-cell lung that consider resistant to the available chemotherapies [8-10].

Quantitative structure-activity relationships models are used to explain a relationship of structural and/or property descriptors of compounds with their biological activities [11]. These descriptors explaining properties like steric, electronic, topologic and hydrophobic of molecules, it have been determined through empirical methods, only more recently by computational methods [12,13].

Computational drug discovery help in identifying potent drug molecules and targets by utilize bioinformatics tools, also used to generate active drug molecules, check for their dynamic and kinetic properties, evaluate the target structures for possible binding/active sites, the docking studies of these molecules with the target molecules will help to know the affinity and efficacy of developed molecule [14]. The molecules which are showing better activity can be modified and build to get good activity towards the target molecules, further optimize the molecules to improve binding characteristics. The use of computational drug design methods will help us in all aspects of drug discovery today and forms the importance of structure-based drug design. There are many programs helping us to build active drug molecules. At the same time, high-performance computing, data management software [15]. The use of computational science in drug discovery increases the chance to succeed in many sides like lead identification and lead optimization, developing a promising molecule against diseases. The drug discovery process using in computational method were easy to perform and lower cost. Recently many attempts took place in order to predict new drugs with best activities based on computational method, also to understand theoretically the drug-receptor interaction process using computational chemistry concepts [16-20].

METHODOLOGY

Data set

Seven β-carboline compounds having promising anticancer activities against esophageal cancer cell have been considered in the present study to the development of Quantitative Structure–activity Relationship (QSAR) models (Table 1). These compounds were synthesized and their IC_{50} have been measured by Frederick et al. [21].

Molecular structure optimization and descriptor calculation

All molecular structures were initially subjected to geometrical optimization using Gaussian 03 at the PM3 level, geometrical optimization provided low-energy conformers in which their output files were consequently used for extracting quantum chemical descriptors. Quantum chemical descriptors consisted of the many physicochemical properties involved; heat of formation ΔHf°, partition coefficient, molar refractivity, HOMO-LUMO energy Gap, Electron Affinity (EA), Ionization Potential (IP), Chemical Hardness (η), The electronegativity (χ) and Global electrophilicity index (ω).

Table 1: Structure and activity (Log IC_{50}) of β-Carboline compounds

Log IC_{50}	Compound name	abbreviation	No
-0.6	7-(benzyloxy)-2-(2-fluorobenzyl)-1-methyl-9-propyl-9H-pyrido[3,4-b]indol-2-ium	βC.1	1
-0.52	2-benzyl-7-(benzyloxy)-1-methyl-9-propyl-9H-pyrido[3,4-b]indol-2-ium	βC.2	2
-0.43	2-benzyl-7-(cyclohexylmethoxy)-9-(cyclohexylmethyl)-1-methyl-9H-pyrido[3,4-b]indol-2-ium	βC.3	3
-0.15	2,9-dibenzyl-7-(benzyloxy)-1-methyl-9H-pyrido[3,4-b]indol-2-ium	βC.4	4
0.146	2-benzyl-9-(4-fluorobenzyl)-7-((4-fluorobenzyl)oxy)-1-methyl-9H-pyrido[3,4-b]indol-2-ium	βC.5	5
0.38	9-benzyl-7-(benzyloxy)-2-(4-fluorobenzyl)-1-methyl-9H-pyrido[3,4-b]indol-2-ium	βC.6	6
0.74	2-benzyl-7-(benzyloxy)-1-methyl-9H-pyrido[3,4-b]indol-2-ium	βC.7	7

QSAR modeling

QSAR are regression models having an important role in the drug design strategies. QSAR regression models relate a set of predictor variables (X) calculated from the physicochemical properties to the potency of the response variable (Y) which is biological activity. In the present study, numbers of different physicochemical descriptors have been taken into consideration to develop QSAR of β-carboline compounds. The drug's potency is here a dependent variable, and the molecular descriptors, are the independent variables.

RESULTS AND DISSCUSSION

Gaussian software, Parametric Method 3 (PM3) was using to minimize the total energy of each derivative and optimizes the equilibrium electronic structure of molecules which related to its physicochemical properties, then selected the properties which found proportional to activity ($LogIC_{50}$) with higher R^2 value, results reported in Tables 2 and 3. The study indicates that for all the set of β-carboline compounds, HOMO orbital is in the core of the compound exactly around the carbazole and indole moieties (Figure 1).

In order to highlight the different physicochemical properties which investigated in this work: The HOMO-LUMO gap, i.e., the difference in energy between the HOMO and LUMO, is an important stability index? A large HOMO-LUMO gap implies high stability for the molecule in chemical reactions [22], IE is defined as the amount of energy required to remove an electron from a molecule. It is related to the energy of the EHOMO through the equation:

$$IE \text{ (Ionization potential)} = -EHOMO$$

Ionization energy is a fundamental descriptor of the chemical reactivity of atoms and molecules. EA is defined as the energy released when an electron is added to a system. It is related to ELUMO through the equation: $EA = -ELUMO$.

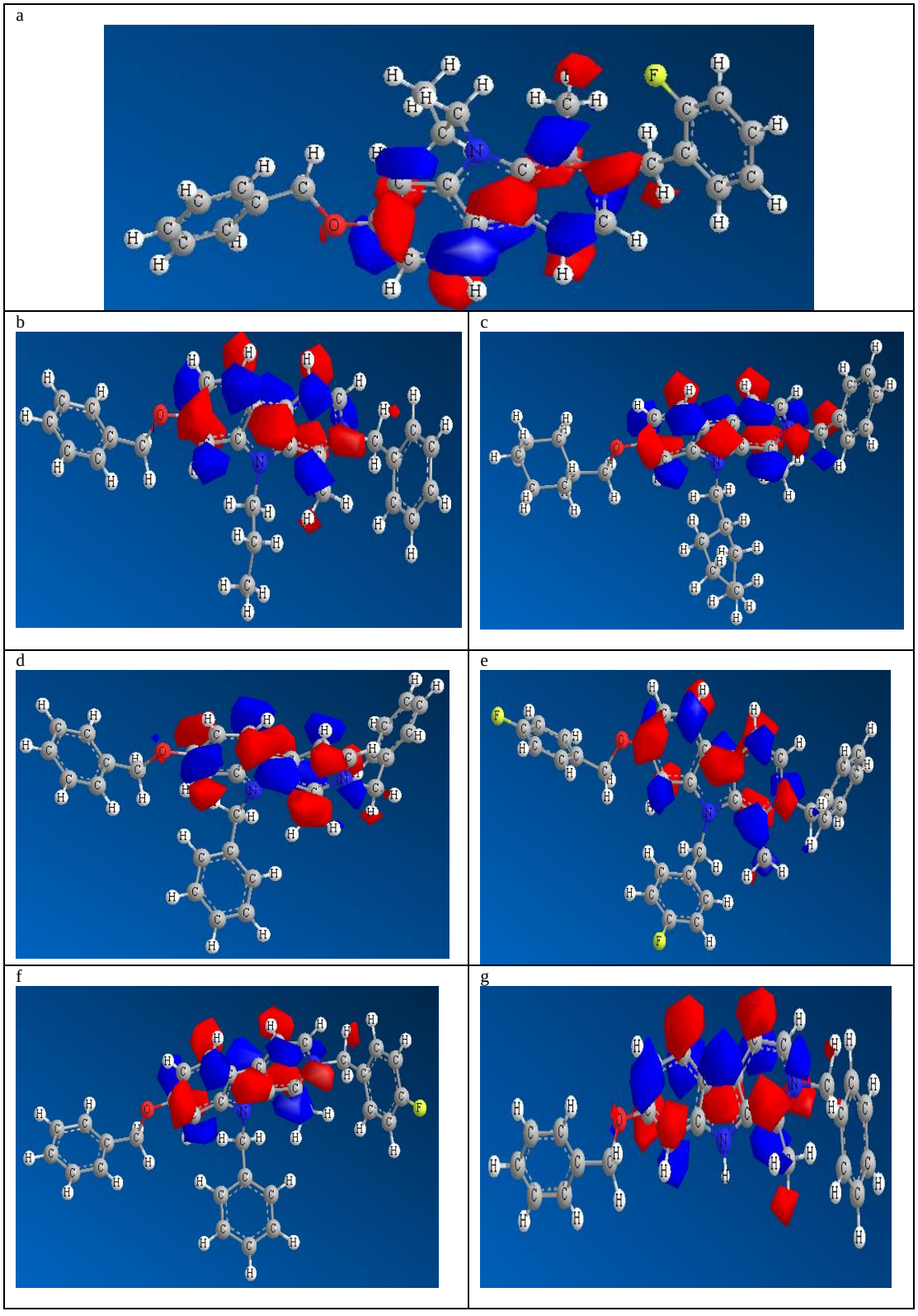

Figure 1: HOMO molecular orbital for a. βC.1, b. βC.2, c. βC.3, d. βC.4 e. βC.5, f. βC.6, g. βC.7

The higher HOMO energy corresponds to the more reactive molecule in the reactions with electrophiles while lower LUMO energy is essential for molecular reactions with nucleophiles [23], chemical hardness (η) measures the resistance of an atom to a charge transfer, it is estimated using the equation: η (Hardness)=(IE−EA)/2. Absolute hardness IS important property to measure the molecular stability and reactivity. It is apparent that the chemical hardness fundamentally signifies the resistance toward the deformation or polarization of the electron cloud of the atoms, ions, or molecules under small perturbation of chemical reaction. A hard molecule has a large energy gap, and a soft molecule has a small energy gap [23], Electronegativity (χ) is the measure of the power of an atom or group of atoms to attract electrons toward its self; it can be estimated using the following equation [24]: χ (electronegativity)=(IE+EA)/2. Global electrophilicity index (ω) shows the ability of the molecules to accept electrons.

It is a measure of the stabilization in energy after a system accepts additional amount of electron charge from the environment. They defined global electrophilicity index (ω): $(\omega)=-x^2/2\eta$. According to the definition, this index measures the propensity of chemical species to accept electrons. A good, more reactive, nucleophile is characterized by lower value of μ, ω and conversely, a good electrophile is characterized by a high value of μ, ω [25].

Table 2: Physicochemical properties of β-carboline compounds

Compound Property	βC.1	βC.2	βC.3	βC.4	βC.5	βC.6	βC.7
ΔHf °/Kcal mol^{-1}	195.25	171.63	189.11	194.13	242.64	222.92	158.22
Partition coefficient	4.019	3.912	3.641	3.398	3.128	2.848	2.605
Molar Refractivity	15.59	15.194	14.869	14.513	13.945	13.329	11.938
ΔE HOMO-LUMO/eV	-1.261	-1.258	-1.252	-1.246	-1.244	-1.239	-1.234
IE /eV	2.251	2.246	2.239	2.227	2.22	2.213	2.206
EA /eV	0.99	0.988	0.987	0.981	0.976	0.974	0.972
η /eV	0.631	0.629	0.626	0.623	0.622	0.619	0.617
χ /eV	1.6205	1.617	1.613	1.604	1.598	1.594	1.589
ω	-2.083	-2.079	-2.078	-2.065	-2.053	-2.049	-2.046
Log IC_{50}	-0.6	-0.52	-0.43	-0.15	0.146	0.38	0.74

Table 3: Linear Regression and correlation coefficient for physicochemical properties of β-carboline compounds

X=Physicochemical properties	Drugs	βC.1	βC.2	βC.3	βC.4	βC.5	βC.6	βC.7
	Y=Log IC_{50}	-0.6	-0.52	-0.43	-0.15	0.146	0.38	0.74
	R^2				Linear regression			
ΔHf /Kcal mol^{-1}	0.004				y=3.651x+ 196.5			
Partition coefficient	0.977				y=-1.045x+ 3.299			
Molar refractivity	0.969				y=-2.446x+ 14.04			
ΔE HOMO-LUMO/eV	0.943				y=0.019x -1.246			
IE/eV	0.960				y=-0.033x+ 2.226			
EA/eV	0.954				y=-0.014x+ 0.980			
η/eV	0.942				y=-0.009x+ 0.623			
χ/eV	0.962				y=-0.023x+ 1.603			
ω	0.942				y=0.029x -2.062			

All parameters should be selected which to be relevant to the activity for the series β-carboline compounds under investigation. Predictor variables are then checked one by one using the partial correlation coefficient as an importance measure in predicting the dependent variable. At each case the variable with the highest significant partial correlation coefficient is added to the QSAR model.

The partial correlation coefficient for any variable is the correlation between the variable and the response when the present independent variables in the equation are held fixed. For each property; select a sharing percent to the activity depending on the slope (S) of properties linearity behavior to activity (Table 4).

An attempt has been made to perform the quantitative structure-activity relationship studies of these derivatives utilizing theoretical molecular descriptors calculated computationally from the structure of these compounds to explore the essential structural requirements to design more potent active β-Carboline compounds having more effective treatment against oseophageal cancer. By applying the values of the calculated properties in QSAR equation:

$$\text{Activity}=\int(\text{properties})+\text{constant} \quad (1)$$

The above equation can be written in another expression: $\text{Activity}=\text{Log}IC_{50}(Y)=a_o \pm \sum \grave{a}_i X_i$ (2);
By applied Hansch model [26]:

$$y=a0+a1D1+a2\ D2+ \ldots\ldots\ldots\ldots..+a\ D \quad (3)$$

Table 4: sharing of selected physicochemical properties to the activity of β-carboline compounds

Property Drug	Partition coefficient $^*S$	Molar refractivity $^*S$	ΔE HOMO-LUMO $^*S$	IE $^*S$	EA $^*S$	χ^*S
βC.1	-4.19986	-38.1331	-0.02396	-0.07428	-0.01386	-0.03727
βC.2	-4.08804	-37.1645	-0.0239	-0.07412	-0.01383	-0.03719
βC.3	-3.80485	-36.3696	-0.02379	-0.07389	-0.01382	-0.0371
βC.4	-3.55091	-35.4988	-0.02367	-0.07349	-0.01373	-0.03689
βC.5	-3.26876	-34.1095	-0.02364	-0.07326	-0.01366	-0.03675
βC.6	-2.97616	-32.6027	-0.02354	-0.07303	-0.01364	-0.03665
βC.7	-2.72223	-29.2003	-0.02345	-0.0728	-0.01361	-0.03655

Where, y-practical activity, a-regression coefficient, D-descriptors (S^* property). The general equation will be:

$$Y = a_0 \pm a_1 \times slop \times X_1 \pm a_2 \times slop \times X_2 \pm a_3 \times slop \times X_3 \pm a_4 \times slop \times X_4 \pm a_5 \times slop \times X_5 \pm a_6 \times slop \times X_6 \quad (4)$$

Where, X1=S^* Partition coefficient, X2=S* Molar refractivity, X3=S*ΔE HOMO-LUMO, X4=S*IE, X5=S*EA and X6=S*

By solving set of mathematical equations [27] using Wolfram Mathematica 7.0 program to find the final activity equation, the value of regression coefficients were: a0=916.052, a1=-15.2251, a2=0.509647, a3=-84691, a4=14820, a5=-227575, a6=135329.

So the final equation of activity is:

$$Y = 916.052 + 15.2251 \times slop \times X_1 - 0.509647 \times slop \times X_2 + 84691 \times slop \times X_3 - 14820 \times slop \times X_4 + 227575 \times slop \times X_5 - 135329 \times slop \times X_6 \quad (5)$$

The activity of each compound has calculated depending on the above results, then Comparisons were made between theoretical and experimental value of activity (Table 5). The comparisons show an excellent linear relation with R^2 and slope of unity (Figure 2).

Table 5: Comparisons between theoretical and experimental value of Log IC_{50}

Compound	Experimental Log IC_{50}	Theoretical Log IC_{50}
βC.1	-0.6	-0.5947
βC.2	-0.52	-0.5147
βC.3	-0.43	-0.4247
βC.4	-0.15	-0.1448
βC.5	0.146	0.1512
βC.6	0.38	0.3852
βC.7	0.74	0.7451

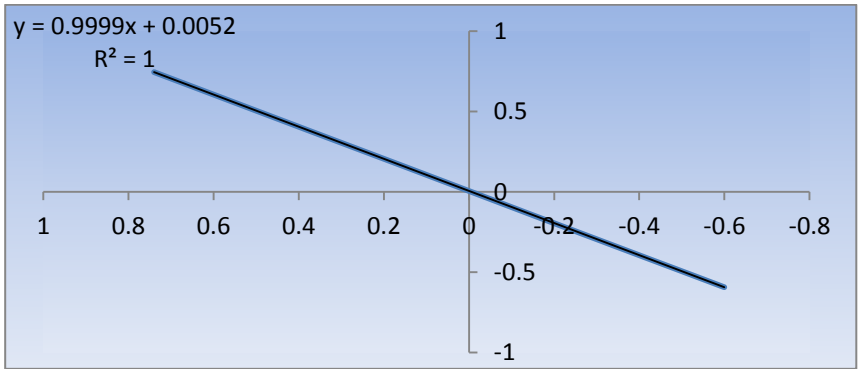

Figure 2: Practical activities (Log IC_{50}) as measured and theoretical activities as calculated

To overcome the intrinsic resistance of cancer cells to apoptotic stimuli, we try to predict a new β-carbolines structurally related to harmine with high activity values than the traded analog compounds, the new compounds show in Figure 3, the physicochemical properties & sharing of these properties to the activity of predicted β-carboline compounds were calculated and listed in Table 6, the activity of each compound were calculated according to equation 5, the theoretical activity values of predicted compounds shown in Table 7.

Table 6: Physicochemical properties and sharing of these properties to the activity of predicted β-carboline compounds

Drug property	N1-βC	N2-βC	N3-βC
Partition coefficient	2.23	2.253	1.17
Molar refractivity	13.36	14.64	12.43
ΔE HOMO-LUMO	-1.298	-1.407	-1.272
IE	2.232	2.22	2.207
EA	0.934	0.813	0.935
χ	1.583	1.5165	1.571
Property*Slope			
Partition coefficient *S	-2.33035	-2.35439	-1.22265
Molar refractivity *S	-32.6786	-35.8094	-30.4038
ΔE HOMO-LUMO *S	-0.02466	-0.02673	-0.02417
IE *S	-0.07366	-0.07326	-0.07283
EA *S	-0.01308	-0.01138	-0.01309
χ*S	-0.03641	-0.03488	-0.03613

Table 7: The structure and the activity of predicted β-carboline compounds

Abbreviation	Compound name	Log IC50
N1-βC	2-(2-fluorobenzyl)-7-((2-fluorobenzyl)oxy)-1-methyl-9-propyl-9H-pyrido[3,4-b]indol-2-ium	-18.93
N2-βC	7-((2-(dimethylamino)benzyl)oxy)-2-(2-fluorobenzyl)-1-methyl-9-propyl-9H-pyrido[3,4-b]indol-2-ium	-18.747
N3-βC	2-(2-fluorobenzyl)-7-((2-fluorobenzyl)oxy)-1,9-dimethyl-9H-pyrido[3,4-b]indol-2-ium	-23.66

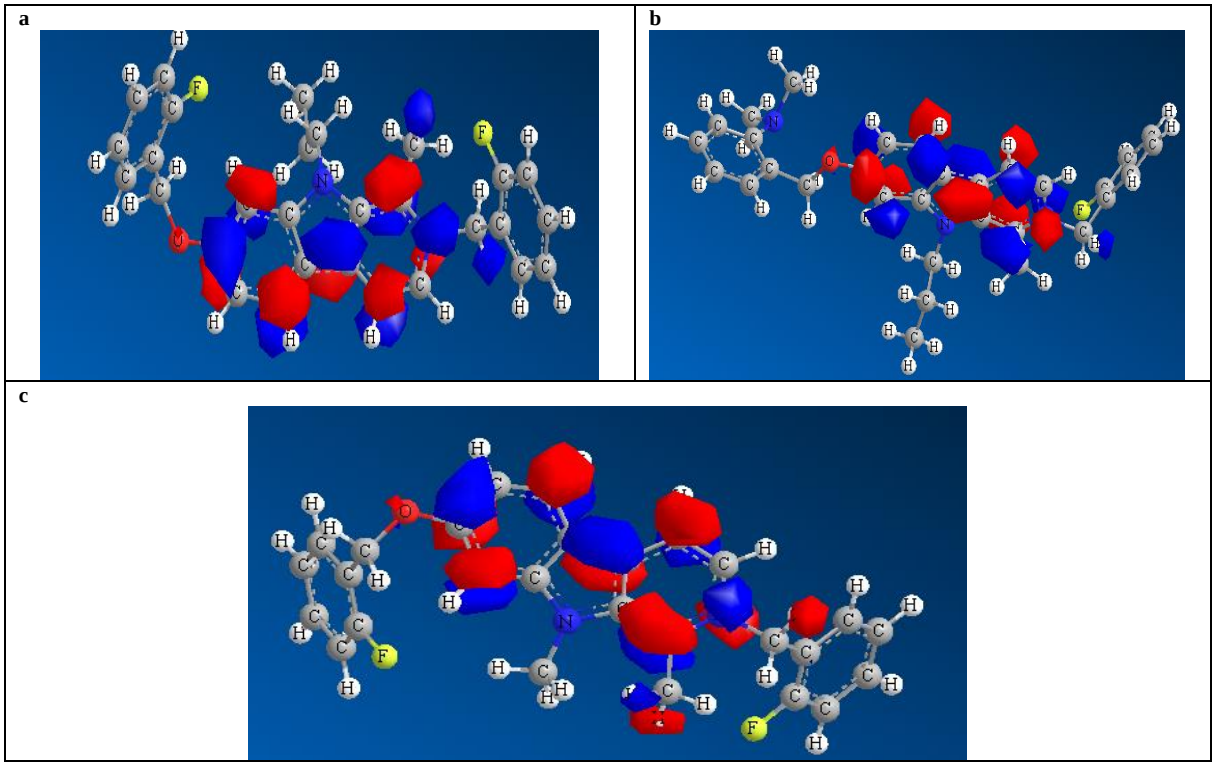

Figure 3: HOMO molecular orbital of predicted compound a. N1-βC, b. N2-βC, c. N3-βC

For the predicted compounds, the results were shown that for the most active molecule βC.1, the introduction of electron-donating group(F) on benzyl substituent at position 2, anti-tumor activities of these compounds were increased dramatically from Log IC_{50}=-0.6 to Log IC_{50}=-18.932 (keep in mind that the term of activity her refers to the minimum effective inhibition concentration).

Replacement of F by tri-methyl amine on benzyl substituent at position 2 reduced the activity from Log IC_{50}=-18.932 in N1-βC to Log IC_{50}=-18.747 in N2-βC. The most interested result is for N3-βC which has the same structure of N1-βC but replacing the propyl group on N-carbazole by methyl group, massive increase have been noted from Log IC_{50}=-18.932 to Log IC_{50}=-23.66, we thought that the reducing of the size of alkyl group may be introduction a suitable interaction with target so the activity increase in that manner.

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