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Quantitative Structure-Activity Relationship Studies of Insecticidal activity of Octahydro-quinazolinone derivatives

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Abstract
The In this work we attempt to establish a quantitative structure-activity relationship (QSAR) for Insecticide activity against *spodoptera litura*., by studying a series of 14 substituted Octahydroquinazolinone and derivatives. Density functional theory calculations (DFT) have been carried out in order to get insights into the structure and property information for this series of molecules. Descriptors such as total energy, Gap energy, HOMO and LUMO energies, dipole moment (μ), electronegativity (χ), global hardness (η), softness (σ), electrophilicity index, partition coefficient, repulsion energy, ovality, log P, boiling point, cluster count and Molecular weight. Provide vital information about the insecticide activity of substituted Octahydroquinazolinone. We accordingly propose a quantitative model based on such calculated parameters to predict the Insect mortality (*S. litura*) by contact and feeding methods, the % Mortality and the % growth inhibition index against *Spodoptera litura*. After, we try to interpret these types of activities relying on the multivariate statistical analyses. The MLR has served to select the descriptors used and also to predict studied activities. The topological descriptors and the electronic descriptors were computed with ACD/ChemSketch and Gaussian 03W program, respectively.

Keywords: Insecticidal activity, Octahydroquinazolinone. Quantitative structure–property relationship, DFT calculations.

1. Introduction

Octahydroquinazolinone derivatives are an important class of the organic compounds which due to their molecular structure, have important biological activities such as antibacterial activity [1, 2] and insecticidal activity against *Spodoptera litura*.

Several methods have been developed for the preparation of Octahydroquinazolinone derivatives. The compounds on which we will perform our study were prepared and studied by A. Akbari et al [3] . These authors have described the detailed synthesis of these derivatives. they in fact prepared the 4-(4-nitro-phenyl)-7,7-Dimethyl-1,2,3,4,5,6, 7, 8-octahydroquinazoline - 2, 5 - dione using 4-nitrobenzaldehyde, dimedone, urea and BF3.SiO2 as the catalyst in 1,2-dichloroethane solvent
On the other hand, *Spodoptera litura* is a pest with a very large capacity to reproduce and the ability to migrate and spread in wide distance, all these reasons makes the *Spodoptera litura* a serious pest who can attacked several agricultural crops, it is known as a pest that can cause significant damage (26 to100% loss) and it can destroy plants such as cotton, soybean, peanut, tobacco and vegetables [4, 5]. *Spodoptera litura* is one of the first pests who developed resistance against the traditional insecticides; it is a significant example of the problems caused by resistance to pesticides. To fight

against, and conquer the resistance of this pest, many new types of insecticides were Played [5, 6]

A.Akbari et al [3] have experimentally studied the in vitro insecticidal activity of these compounds, the bioassay was conducted against the third instar larvae of *S. litura* (ages 7 ± 1 day) by using the method of feeding and topical treatment [7]. While the regulatory activity of insect growth (IGR) IGR activity of the synthesized compounds was evaluated against *S. litura* following a procedure described in the same article.

The objective of this study was to propose predictive QSAR models of 3 types of insecticidal activities of octahydroquinazolinones and derivatives against *spodoptera litura* by using severals statisticals methods.

On the other hand, several quantum chemical methods and Quantum-chemistry calculations have been performed in order to study the molecular structure and the reaction mechanisms in order to interpret the experimental results as well as to solve chemical ambiguities and to correlate the biological activities to the molecular properties [8]. The structure and electronic parameters can be obtained by means of theoretical calculations using the computational methodologies of quantum chemistry. The geometry of the studied molecules in its ground state, as well as the nature of their molecular orbitals, HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are involved in the properties of the activity of inhibitors [9,10].. The relationships between the structural parameters and these biological activities of those compounds have not been studied yet. The activities effects of Octahydroquinazolinone and derivatives depend on their physical and chemical properties, and it is therefore important to recognize the structure–property relationships that allow a complete understanding of their environmental consequences. Hence, in the present study, the molecular structures of substituted Octahydroquinazolinone have been studied. Quantitative structure-activity relationships are generally used to evaluate and predict the "activity" and other properties. The structures of the studied compounds are shown in (**Fig 1).**

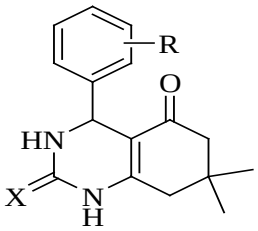


Fig. 1: Studied compounds (Table 1)

The more relevant molecular properties are the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), energy gap (ΔE), dipole moment (μ), the absolute electronegativity (χ) wich is the power of an atom in a molecule to attract the electron, it is a very useful concept for the explanation or understanding of chemical reactivity. [11.12] ,The electrophilicity index (ω) is estimated using the parameters electronegativity and chemical hardness, partition coefficient (K_{OW}), logP, which is a measure of differential sollubility of chemical compounds in two solvents (octanol / water partition coefficient), this value helps apprehend the hydrophilic or lipophilic character of the molecule. [13] Molecular weight (MW) among the descriptors, this is the simplest and most used molecular descriptor, calculated as the sum of the atomic weights. It is related to molecular size and is atom-type sensitive. Ovality (O), is an anisometry descriptor, a measure of the departure of a molecule from The spherical shape, based on the property that fixe the volume, the spherical shape presents the minimum surface [14.15]. It is calculated from the ratio between the actual molecular surface area SA and the minimum surface area SAO corresponding to the actual molecule + van der Wads volume VvDw. the steric energy for frame (SE), Boiling point (Bp) , Cluster count (CC), The Total Energy (*TE*), Repulsion Energy (*RE*), Global hardness (η), Softness (σ) and the Electronic energy (*EE*).

2. Computational details

DFT (density functional theory) methods were used in this study. These methods have become very popular in recent years because they can reach exactitude similar to other methods in less time and less expensive from the computational point of view. In agreement with the DFT results, energy of the

fundamental state of a polyelectronic system can be expressed through the total electronic density, and in fact, the use of electronic density instead of wave function for calculating the energy constitutes the fundamental base of DFT [16]. All calculations were done by GAUSSIAN 03 W software [17] using the B3LYP functional [18] and a 6-31G* basis set [19]. The B3LYP, a version of DFT method, uses Becke's three-parameter functional (B3) and includes a mixture of HF with DFT exchange terms associated with the gradient corrected correlation functional of Lee, Yang, and Parr (LYP). The geometry of all species under investigation was determined by optimizing all geometrical variables without any symmetry constraints. Frontier molecular orbital's (HOMO and LUMO), the ionization potential, $I = -E_{HOMO}$, and the electron affinity, $A = -E_{LUMO}$, the absolute electronegativity, $\chi = \frac{I + A}{2}$, and absolute hardness, $\eta = \frac{I - A}{2}$ and the softness $\sigma = \frac{1}{\eta}$ were calculated from the DFT optimized structures for each molecule. The topological descriptors and some electronic descriptors were computed with ACD/ChemSketch and Gaussian 03W program, respectively.

The multiple linear regression statistic technique is used to study the relation between one dependent variable and several independent variables. It is a mathematic technique that minimizes differences between actual and predicted values. The multiple linear regression model (MLR) was generated using the software XLSTAT [20], The Linear Regression method belongs to a larger family of models called GLM (Generalized Linear Models)

3. Results and discussion

3.1Experimental results

The results reported by A. Akbari et al, [3] on the insecticidal activity of the substituted Octahydroquinazolinone and derivatives against *Spodoptera litura* by two methods: feeding and contact methods show that the percentage of inhibition increases with increasing the number of the hydroxyl and methoxy groups, by consequence the compound 8 shows a moderated activity due to the presence of a one hydroxyl and a methoxy group. The insect growth regulation was also evaluated, and the result shows that the IGR increases by replacing 2-thioxo with 2,5-dione. The results are summarised in (**Table 1)**

Table 1: Chemical structure and observed activities of studied compounds

Compound	R	X	Insect mortality (*S. litura*) (contact)	Insect mortality (*S. litura*) (feeding)	% Mortality	% Growth nhibition index
1	4-OHC$_6$H$_4$	O	65	70	20	80
2	4-OMeC$_6$H$_4$	O	66	62	40	77
3	4-ClC$_6$H$_4$	O	51	58	5	71
4	4-FC$_6$H$_4$	O	47	55	45	75
5	4-NO$_2$C$_6$H$_4$	O	47	48	30	58
6	C$_6$H$_5$	O	39	35	10	47
7	4-BrC$_6$H$_4$	O	53	33	15	53
8	4-OH,3-OMeC$_6$H$_3$	O	78	100	20	100
9	4-OMeC$_6$H$_4$	S	90	85	40	96
10	4-ClC$_6$H$_4$	S	83	78	10	93
11	3-ClC$_6$H$_4$	S	73	72	20	72
12	4-NO$_2$C$_6$H$_4$	S	55	55	30	65
13	C$_6$H$_5$	S	47	42	10	52

14	**4-BrC_6H_4**	**S**	**58**	**48**	**20**	**68**

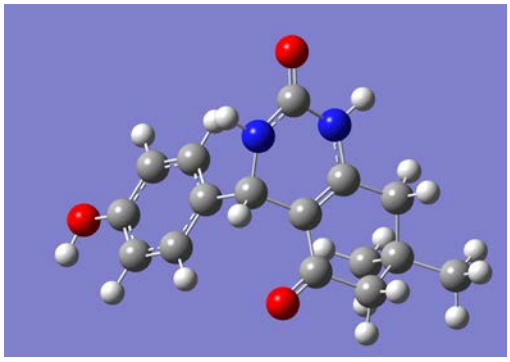
3. 2. Theoretical results
3.2.1 DFT calculations.

On the other hand, quantum chemical calculations were performed to investigate the structural parameters that affect the activities of the studied compounds. Geometric and electronic structures of these molecules were calculated by the optimization of their structures. The obtained theoretical results from the DFT calculations are given in (**Fig 2)** and the obtained HOMO and LUMO orbitals are also presented in (**Fig 3)**. A QSAR study was carried in order to determine a quantitative relationship between chemical structure and biological activity. The (**table 2)** shows the values of the calculated parameters and obtained descriptors.
When analyzing the different results, interesting findings were observed:
The experimental results show that:
The molecules 4, 2 and 9 having respectively in their structure, the groups Fluor and OMe-C6H5 have the best rate in% of mortality. This is probably due to the pi-donor character by mesomerism of Fluor and methoxy. On the other hand the molecules 8, 9, 10 and 1 have the best rate of % Growth inhibition index, always due to the resonance reasons of mesomerism through methoxy groups in conjugation with the pi-electrons of the benzene ring. Therefore, these results presented by A. Akbari et al clearly show that compound 9 possesses the best rate either in terms of % mortality or Growth inhibition index.

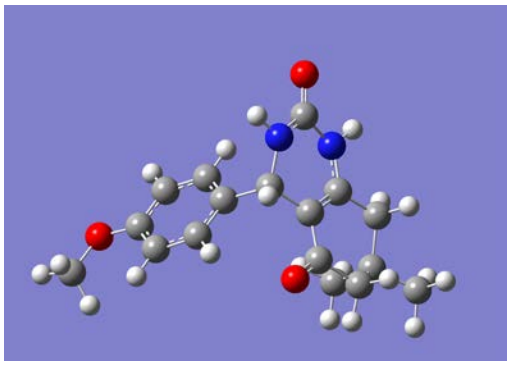
Table 2: The calculated quantum chemical parameters and descriptors of the studied molecules

Molécules	SE (Kcal/mole)	Bp (K)	CC	EE (ev)	log P	MW (Atomic mass unit)	K_{OW} (octanol/Water)	O	RE (Ev)	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	μ (Debye)	TE (u.a.)	η (ev)	σ (ev)	χ (ev)	ω (ev)	Insect mortality (Contact)	Insect mortality (feeding)	% Mortality	% Growth inhibition index
M1	50.72	853.45	27	-34358.6	2.09	362.43	3.33	1.56	29868	-5.84	-1.25	-4.59	3.27	-955.75	-2.295	-0.435	-3.545	-14.420	65	70	20	80
M2	48.74	842.27	28	-37054.4	2.35	376.45	3.916	1.59	32404.5	-5.75	-1.22	-4.53	3.12	-995.05	-2.265	-0.441	-3.485	-13.754	66	62	40	70
M3	44.50	837.31	27	-34897.2	3.04	380.87	4.71	1.56	30363.1	-6.36	-1.08	-5.28	4.35	-1340.13	-2.64	-0.378	-3.72	-18.266	51	58	5	71
M4	51.01	815.94	27	-35152.1	2.64	364.42	4.14	1.55	30506.7	-6.28	-1.37	-4.91	3.93	-979.76	-2.455	-0.407	-3.825	-17.959	47	55	45	75
M5	93.60	881.98	29	-38762.4	2.95	391.42	3.74	1.58	33757	-6.63	-2.35	-4.28	6.79	-1085.03	-2.14	-0.467	-4.49	-21.571	47	48	30	58
M6	43.03	818.62	26	-32882.1	2.48	346.43	3.997	1.54	28708	-6.31	-1.52	-4.79	3.71	-880.29	-2.395	-0.417	-3.915	-18.354	39	35	10	47
M7	43.62	849.32	27	-34814.9	3.31	425.32	4.86	1.57	30301.2	-6.33	-1.56	-4.77	4.3	-3451.63	-2.385	-0.419	-3.945	-18.558	53	33	15	53
M8	44.49	877.11	29	-39911	1.96	392.45	3.1792	1.59	34940.5	-6.3	-1.49	-4.81	3.2	-1454.64	-2.405	-0.415	-3.895	-18.243	78	100	20	100
M9	66.79	851.69	28	-36708.5	3.78	392.52	4.084	1.6	32185.1	-5.78	-1.64	-4.14	4.37	-1318.01	-2.07	-0.483	-3.71	-14.245	90	85	40	96
M10	62.55	846.74	27	-34558.8	4.46	396.94	4.878	1.58	30151.1	-6.08	-1.85	-4.23	4.63	-1663.08	-2.115	-0.472	-3.965	-16.625	83	78	10	93
M11	64.93	846.74	27	-34468.1	4.46	396.94	4.878	1.58	30060.7	-6	-1.83	-4.17	4.72	-1663.08	-2.085	-0.479	-3.915	-15.978	73	72	20	72
M12	111.51	891.41	29	-38425.7	3.46	407.49	3.908	1.59	335.74	-6.42	0.03	-6.45	6.74	-1407.99	-3.225	-0.310	-3.195	-16.460	55	55	30	65
M13	61,08	828,04	26	-32547,1	3,909	362,49	4,165	1,56	28499,5	-5,91	-1,71	-4,2	4,05	-1203,49	-2,1	-0,47	-3,81	-15,241	47	42	10	52
M14	61,30	858,74	27	-34426,9	4,73	441,39	5,028	1,58	30039,7	-6,04	-1,85	-4,19	4,6	-3774,59	-2,095	-0,477	-3,945	-16,302	58	48	20	68

To explain further, trying to propose a model for this we made the following calculations by DFT and QSAR studies. So with the aim to find a mathematical model that can collect the parameters influencing the desired biological activity. Quantum chemical parameters are obtained from the calculations which are responsible for the "activity" of our molecules such as the energies of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), energy gap (ΔE), dipole moment (μ), electronegativity (χ), global hardness (η), softness (σ), and the total energy (*TE*) are collected in (**Table 2).**



M1



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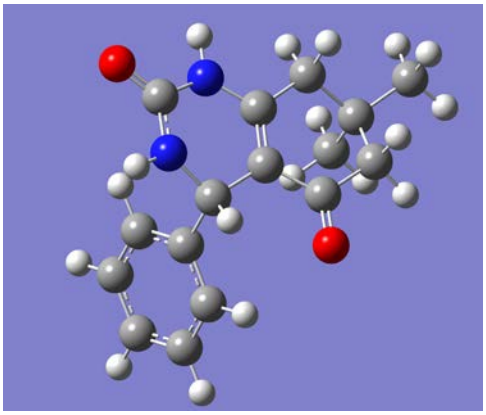
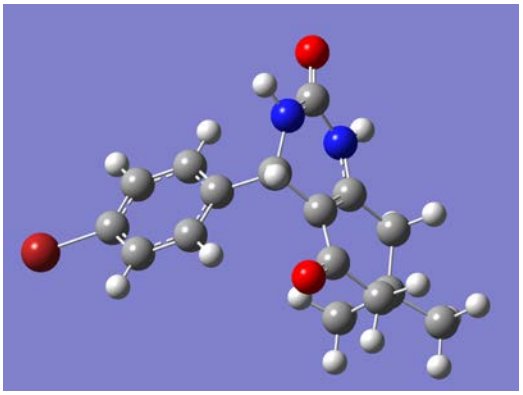
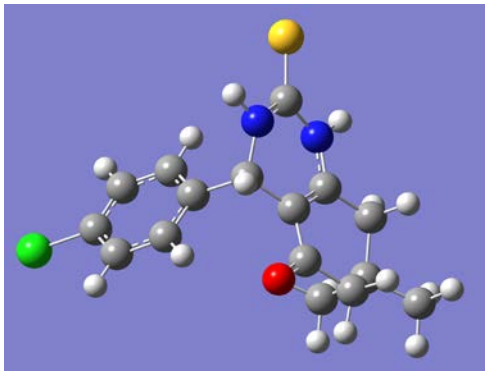


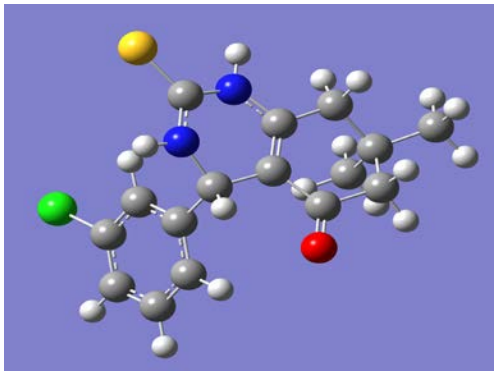
M6



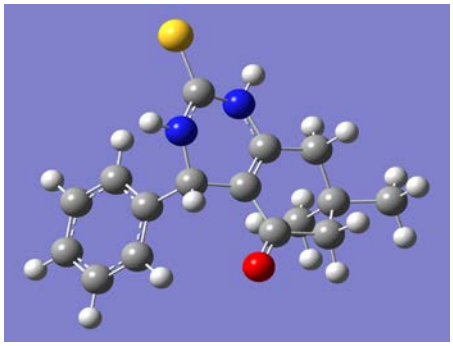
M7



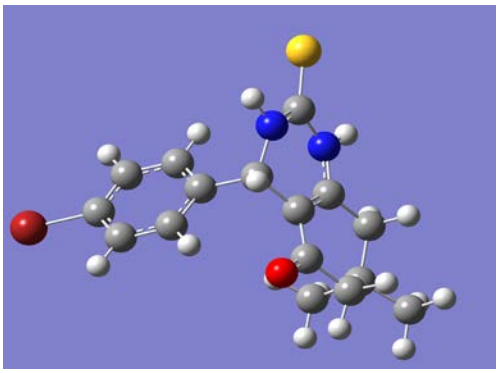
M9



M11



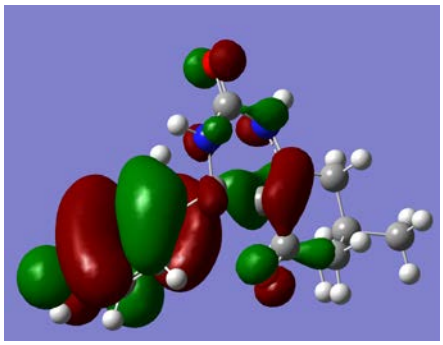
M13

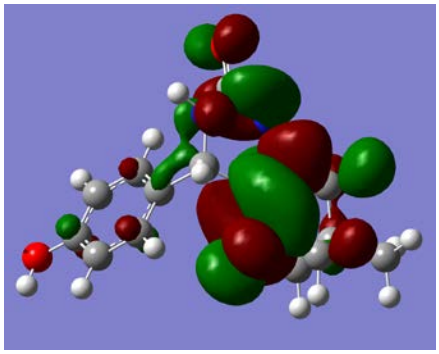


M14

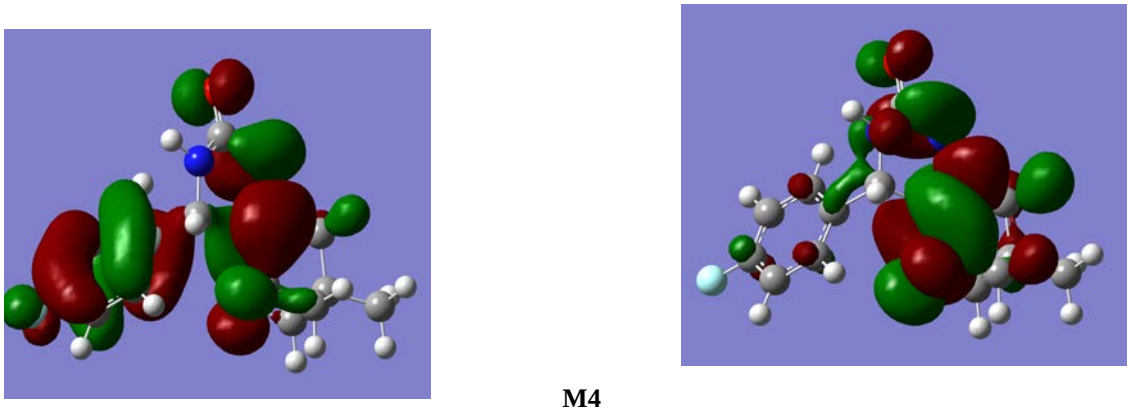
Fig.2. Some obtained molecular structures of the studied molecules

HOMO **LUMO**

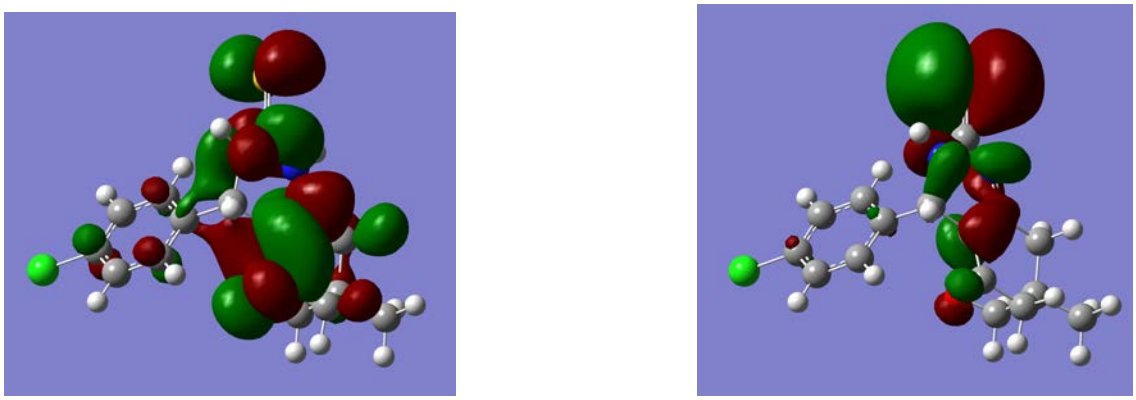




M1



M4



M10

Fig.3. The obtained HOMO and LUMO orbitals of the studied molecules M1, M4 et M10 by DFT/B3LYP/6-31G (d).

3.2.2 Multiple linear regressions

We have set up a model for calculating the "activity" of the studied molecules. This model has been suggested including as many possible descriptors to increase the probability of a good characterization of the studied compounds. We conducted a QSAR study using the method of linear regression between Insecticidal activities against *Spodoptera litura* (contact and feeding methods) also between IGR activities (% Mortality and % Growth Inhibition index) also descriptors used in this work for linear models, Among these descriptors selected using Multiple linear regressions in the study, 10 descriptors reflected the overall characters of our molecules.

The Model equations are:

Insect mortality (contact) = 6558.562 + 1.190 10-02 (EE) + 35.698 log P + 4.586 (MW) - 45.296 (Kow) - 9.124 10-03 (RE) + 1965.626 LUMO + 1765.686 Gap – 35.053 (μ), + 0.109 (TE)– 234.619 (χ).

Insect mortality (feeding) = -1456.895 – 1.922 (SE) – 0.800 (Bp) +1.508 10-02 (EE) + 11.167 log P + 5.015 (M.W) – 74.502 (Kow) – 354.012 LUMO – 307.313Gap + 0.112 (TE) + 35.587 (ω).

IGR (% Mortality) = 207.517 + 1.221 (SE)– 1.772 (Bp) + 7.1529 10-03(EE)– 24.730 log P +

2.699(MW)– 28.026 (Kow)+ 420,688 (O) – 7.454 (μ)+ 3.952 10-02 (TE) – 21.696 (χ).

IGR (% Growth Inhibition index) = -78.493 – 1.502(SE) – 1.345 (Bp) + 2.015 10-02 (EE) + 12.480 log P + 6.068(MW)– 93.550(Kow)– 47.994 HOMO + 0.125 (TE).

From the positive and negative symbols of the coefficients of the variables, we can evaluate the effects of each variable on activity:

The proposed model of the calculated Insect mortality (contact) is described by a linear relationship with Electronic Energy; log P, Molecular Weight, Partition Coefficient, Repulsion Energy, LUMO, Gap energy, Dipole moment, Total Energy, and Electrophilicity.

The Insect mortality (contact) values of the studied molecules increases with increasing LUMO, Gap, and log P and decreasing Electrophilicity, dipole moment and Partition Coefficient.

The proposed model of the calculated Insect mortality (feeding) is described by a linear relationship with the steric energy, boiling point, and Electronic energy, log P, Molecular Weight, Partition Coefficient, LUMO, Gap Energy, Total Energy, and Electrophilicity. The Insect mortality (feeding) values of the studied molecules increases with increasing Electrophilicity and log P and decreasing LUMO, Gap and Partition Coefficient.

The proposed model of the calculated IGR (% Mortality) is described by a linear relationship with the steric energy, boiling point ,electronic energy , log P , Molecular Weight , Partition Coefficient , Ovality , dipole moment , Total Energy and electronegativity. The IGR (% Mortality) values of the studied molecules increases with increasing ovality and decreasing logP, Electronegativity and Partition Coefficient.

The proposed model of the calculated IGR (% Growth Inhibition index) is described by a linear relationship with steric energy, boiling point, Electronic Energy, log P, Molecular Weight, Partition Coefficient, HOMO and Total Energy. The (% Growth Inhibition index) values of the studied molecules increases with increasing log P and decreasing Partition Coefficient and HOMO energy.

The values of the coefficients of all the 10 descriptors and the calculated and experimental values of the insecticidal activity and IGR are listed in (**Table 3)**

Table 3: Coefficients of descriptors.

Insecticidal activity *contact method*

R^2	**0.992**
R^2 adjusted	**0.967**
MCE	**7.761**
Pr > F	**0.006**
F	**39.382**
MAE	**0.96**
MSE	**1.66**
MAPE	**3.4%**

Insecticidal activity *feeding method*

R^2	**0.999**
R^2adjusted	**0.997**
MCE	**0.981**
Pr > F	**0**
F	**490.892**
MAE	**0.35**
MSE	**0.21**
MAPE	**1.38%**

IGR *(% mortality)*

R^2	***0.989***
R^2adjusted	***0.954***
MCE	***7.453***
Pr > F	***0.01***
F	***27.708***
MAE	***0.81***
MSE	***1.59***
MAPE	***10.83%***

IGR (*% Growth Inhibition index)*

R^2	**0.964**
R^2adjusted	**0.906**
MCE	**25.525**
Pr > F	**0,003**
F	**16.62**
MAE	**1.75**
MSE	**9.11**
MAPE	**4.68%**

For the all compounds, the correlation between calculated and experimental insecticidal activity and IGR values is very significant **(Table 3),** as indicated by R^2 value. A plot between the experimental and calculated property values provide a correlation coefficient R^2 value of 0.992, 0.999, 0.989 and 0.964, which reveals the fact that those models can be effectively used as descriptors in the property prediction (**Table 4**) and the graphic representations of the observed activities depending on the predicted activities by the LMR for The four activities are the following. **(Fig4).**

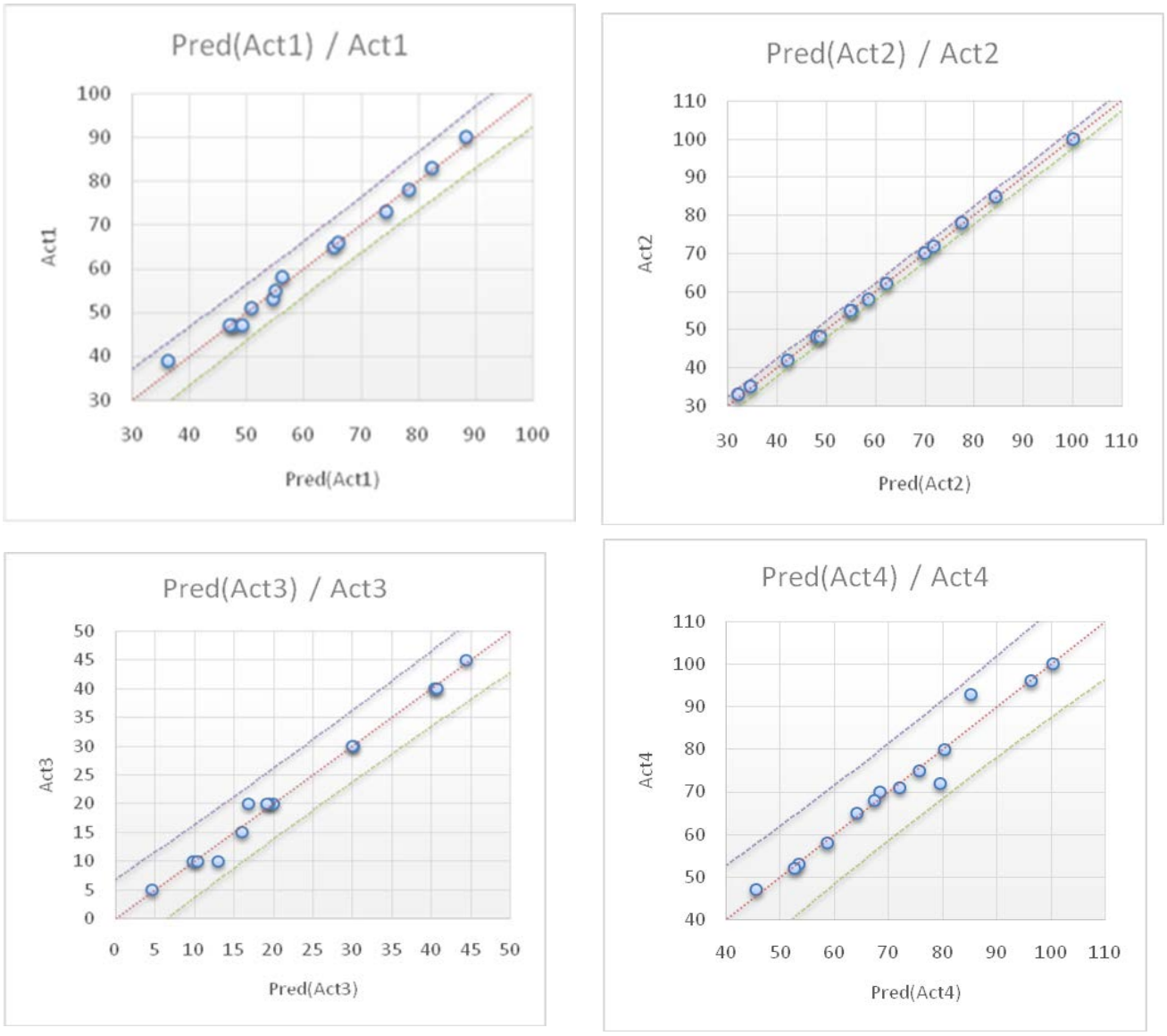


Figure 4: **The graphic representations of the observed activities depending on the predicted activities by the LMR for The four activities,** *Act 1 = Insecticidal activity contact, Act 2 = Insecticdal activity feeding , Act 3= IGR (% mortality), Act 4 = IGR (% Growth Inhibition index).*

Table 4: Plot of calculated and experimental insecticidal activity of the studied compounds

	Insecticidal activity contact	*Pred(Insecticidal activity contact)*	*Residu*		*Insecticdal activity feeding*	*Pred (Insecticdal activity feeding)*	*Residu*		*IGR (% mortality)*	*Pred(% mortality)*	*Residu*		*IGR (% Growth Inhibition index)*	*Pred(% Growth Inhibition index)*	*Residu*
1	*65*	*65 .223*	*-0.223*		*70*	*70.115*	*-0.115*		*20*	*19.951*	*0.049*		*80*	*80.309*	*-0.309*
2	*66*	*66.073*	*-0.073*		*62*	*62.254*	*-0.254*		*40*	*40.450*	*-0.450*		*70*	*68.498*	*1.502*
3	*51*	*50.811*	*0.189*		*58*	*58.528*	*-0.528*		*5*	*4.627*	*0.373*		*71*	*72.073*	*-1.073*
4	*47*	*47.613*	*-0.613*		*55*	*55.300*	*-0.300*		*45*	*44.398*	*0.602*		*75*	*75.646*	*-0.646*
5	*47*	*47.117*	*-0.117*		*48*	*48.155*	*-0.155*		*30*	*30.126*	*-0.126*		*58*	*58.744*	*-0.744*
6	*39*	*36.363*	*2.637*		*35*	*34.675*	*0.325*		*10*	*9.864*	*0.136*		*47*	*45.559*	*1.441*
7	*53*	*54.572*	*-1.572*		*33*	*32.057*	*0.943*		*15*	*16.062*	*-1.062*		*53*	*53.451*	*-0.451*
8	*78*	*78.434*	*-0.434*		*100*	*100.067*	*-0.067*		*20*	*19.475*	*0.525*		*100*	*100.416*	*-0.416*
9	*90*	*88.361*	*1.639*		*85*	*84.307*	*0.693*		*40*	*40.724*	*-0.724*		*96*	*96.367*	*-0.367*
10	*83*	*82.487*	*0.513*		*78*	*77.661*	*0.339*		*10*	*12.959*	*-2.959*		*93*	*85.127*	*7.873*
11	*73*	*74.393*	*-1.393*		*72*	*71.961*	*0.039*		*20*	*16.840*	*3.160*		*72*	*79.543*	*-7.543*
12	*55*	*54.992*	*0.008*		*55*	*54.886*	*0.114*		*30*	*29.999*	*0.001*		*65*	*64.090*	*0.910*
13	*47*	*49.298*	*-2.298*		*42*	*42.114*	*-0.114*		*10*	*10.411*	*-0.411*		*52*	*52.737*	*-0.737*
14	*58*	*56.264*	*1.736*		*48*	*48.922*	*-0.922*		*20*	*19.115*	*0.885*		*68*	*67.440*	*0.560*

4. Conclusions

In this paper, the molecular structures of substituted Octahydroquinazolinone have been studied. Quantitative structure-activity relationships are generally used to evaluate and predict the "activity" and other properties. Geometric and electronic structures of these molecules were calculated by the DFT optimization of their structures.. A QSAR study was carried in order to determine a quantitative relationship between structure chemical and biological activity (Insect mortality (contact), Insect mortality (feeding), IGR (% Mortality) and IGR (% Growth Inhibition index). We have established a relationship between several descriptors and those activities in satisfactory manners. The good results obtained with the validation, shows that the proposed model for each property is able to predict activity with a great performance, and that the selected descriptors are pertinent. The accuracy and predictability of the proposed models were illustrated by the comparison of key statistical terms like R or R2 of different models obtained by different descriptors has been shown in **(Table 3)**. It was also shown that the proposed methods are a useful aid for reduction of the time and cost of synthesis activity determination of organic molecules and especially in this study Insecticide activity of Octahydroquinazolinone derivatives.

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