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QSAR analyses of Octahydroquinazolinone for insecticidal activity against spodoptera litura and its in-silico validation using molecular Docking study.

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Abstract

In order to establish a quantitative structure-activity relationship (QSAR) for Insecticide activity against spodoptera litura, we have, first, studied a series of 14 substituted Octahydroquinazolinone and derivatives by using Density functional theory calculations (DFT) .To get insights into the structure and property information for this series of molecules and to better understanding the relationship between structure and activity, we have used Molecular Docking method. 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, The MLR has served to select those descriptors and also to propose a quantitative model based on such calculated parameters to predict insect mortality (S. litura) by contact and feeding methods, and the % growth inhibition index against Spodoptera litura. After, we try to interpret these types of activities. The topological and the electronic descriptors were computed with ACD/ChemSketch and Gaussian 03W program, respectively.

Keywords: *QSAR, Molecular Docking, Octahydroquinazolinon, DFT, insecticide activity.*

1. Introduction

Octahydroquinazolinone derivatives are an important class of the organic compounds that possess interesting properties and 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., it should be noted that the 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]. On the other hand, Spodoptera litura is one of the first pests that developed resistance against the traditional insecticides; it is a significant example of the problems caused by resistance to pesticides. To fight against, the resistance of this pest, many new types of insecticides were Played [5, 6]. 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 and they have 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 paper. The objective of this study, is firstly, to propose predictive QSAR models of 3 types of insecticidal activities of octahydroquinazolinones and derivatives against spodoptera litura by using severals statisticals methods and then we have used Molecular Docking method to better understanding the relationship between structure and activity. To do this, we have used statistical methods and Quantum-chemistry calculations to study the molecular structure and to correlate the biological activities to the molecular properties. The structure and electronic parameters can be obtained by means of theoretical calculations using the computational methodologies of quantum chemistry [8]. 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 interaction effect may be predict by using molecular docking that help out for predicting designed molecule's activity with respect to binding site. The structures of the studied compounds are shown in (Figure 1).

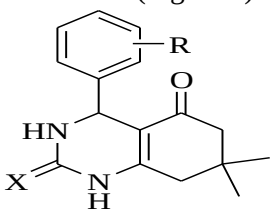


Figure 1: studied compound

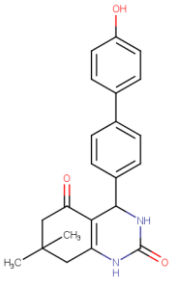
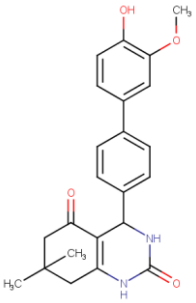
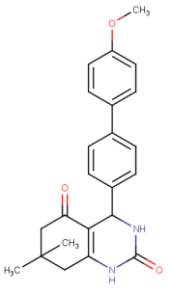
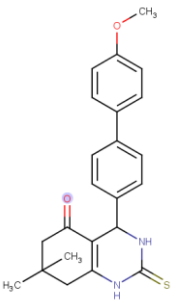
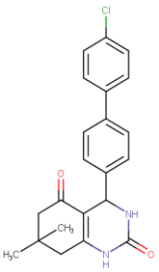
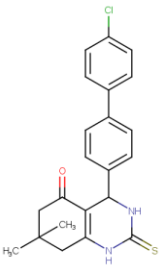
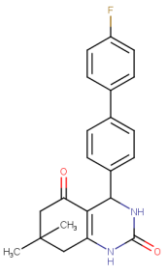
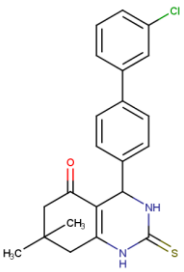
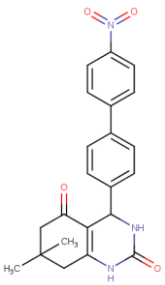
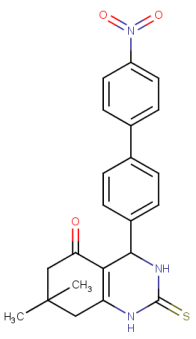
2. Materials and methods

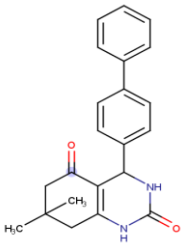
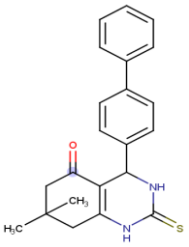
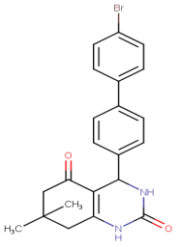
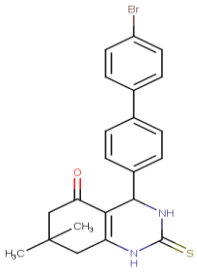
2.1 Chemical data

A dataset of the series of octahydroquinazolinone compounds collected from literature [3] , are listed in Table 1 . A total of 14 derivatives of octahydroquinazolinone , were studied and analyzed in order to find quantitative structure

activity relationship between the insecticide activity and the structure of these molecules. All the molecules are drawed using marvinsketch program [11].

Table 1: Chemical structure of studied compounds (octahydroquinazolinone derivatives)

SN	Structure	SN	Structure
M1		M8	
M2		M9	
M3		M10	
M4		M11	
M5		M12	

M6		M13	
M7		M14	

2.2 Density Functional Theory (DFT):

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 [12]. All calculations were done by GAUSSIAN 03 W software [13] using the B3LYP functional [14] and a 6-31G* basis set [15]. 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. Electronique descriptors were calculated from the DFT optimized structures for each molecule.The topological descriptors were computed with ACD/ChemSketch and Chemdraw 8.0 Programms.

2.3 Multiple Linear Regressions (MLR):

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 2014 [16], The Linear Regression method belongs to a larger family of models called GLM (Generalized Linear Models).

2.4 Molecular Docking:

The docking model and scoring functions have been extensively studied in recent years, and many scoring functions have been proposed [17]. Neurotoxics remain the most important class which corresponds to more than 75% of the worldwide market for insecticides [18]. They act on the nervous system of insects by disrupting synaptic transmission. Among the target of the insecticide widely studied are insect nicotinic acetylcholine receptor [19] .The crystal structure of the acetylcholine binding protein (AChBP) from Lymnaea stagnalis (Ls-AChBP) in complex with imidacloprid (IMI) (PDB: 2ZJU) [20] was used for the molecular docking studies because there is still no crystal structure of nAChR of insect spodoptera litura and Ls-AChBP has high homology to the extracellular domain of nAChR. Actually, Ls-AChBP has been used to study the interaction between compounds with nAChR. [21, 22]. In

this work, we used the Autodock Vina program to carry out the molecular docking studies. The ligands and protein preparation steps (adding polar hydrogen to the protein and deleting the water molecules) for the docking protocol were carried out in Autodock tools 1.5.4 from MGL Tools package, The bioactive conformations were simulated using Autodock vina. [23]. The results were analyzed using Discovery studio 2016. [24] and PyMol [25] software's.

3. Results and Discussions

3.1 Experimental results

The insect mortality and The IGR activity of the above synthesized compounds was evaluated against S. litura by Akbari et al [3]. The procedure and 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 summarized in (Table 2).

Table 2: Observed activities of studied compounds

Compound	IMC	IMF	IGR
M1	**65**	**70**	**80**
M2	66	62	77
M3	51	58	71
M4	47	55	75
M5	47	48	58
M6	39	35	47
M7	53	33	53
M8	**78**	**100**	**100**
M9	**90**	**85**	**96**
M10	**83**	**78**	**93**
M11	73	72	72
M12	55	55	65
M13	47	42	52
M14	58	48	68

Insect mortality by contact (IMC), Insect mortality by feeding (IMF), IGR (% Growth Inhibition index) When analyzing the experimental results, interesting findings were observed: The molecules 8, 9, 10 and 1 have the best rate of % Growth inhibition index, 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 % insect mortality or Growth inhibition index.[3]

3.2 Theoretical results

3.2.1 QSAR Model

To explain further, trying to propose a model for these results, we made the following calculations by DFT and QSAR studies. So with the aim to find a mathematical model, 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 (EHOMO), energy of lowest unoccupied molecular orbital (ELUMO), energy gap (ΔE), dipole moment (μ), electronegativity (χ), global hardness (η), softness (σ), and the total energy (TE) are collected We have, firstly 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. Detailed calculations of descriptors and different used methods have been already published by our team [26]. We have conducted a QSAR study using the method of linear regression between Insecticidal activities against Spodoptera litura (contact and feeding methods) also between IGR activities (% 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:

IMC = 6558.562 + 1.190 10-02 (EE) + 35.698 (logP) + 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).

IMF = -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 = -78.493 – 1.502 (SE) – 1.345 (Bp) + 2.015 10-02 (EE) + 12.480 (logP) + 6.068(MW) – 93.550(Kow) – 47.994 (HOMO) + 0.125 (TE).

Statistical values obtained by MLR for different activities are listed in (Table 3)

Table 3: Statistical values obtained by MLR for different activities

	IMF	**IMC**	**IGR**
R	0.99	0.99	0.98
R^2	0.99	0.99	0.96
MSE	0.21	1.66	0.21
MAE	0.35	0.96	1.75
F	490.89	39.38	16.62

Correlation coefficient (R), Mean squared error (MSE), Mean Absolute Error (MAE), determination coefficient (R^2), Fisher's criterion (F), Insect mortality by contact (IMC), Insect mortality by feeding (IMF), IGR (% Growth Inhibition index). For the all compounds, the correlation between calculated and experimental insecticidal activity and IGR values is very significant (Table 3), as indicated by R and R2 value. A plot between the experimental and calculated property values provide a correlation coefficient R2 value of 0.992, 0.999 and 0.964, which reveals the fact that those models can be effectively used as descriptors in the property prediction (Table 4).

Table 4 : Calculated and experimental insecticidal activity of the studied compounds

	IMC	*Pred(IMC)*	*Residu*	*IMF*	*Pred(IMF)*	*Residu*	*IGR*	*Pred(IGR)*	*Residu*
1	65	65,223	-0,223	70	70,115	-0,115	80	80,309	-0,309
2	66	66,073	-0,073	62	62,254	-0,254	70	68,498	1,502
3	51	50,811	0,189	58	58,528	-0,528	71	72,073	-1,073
4	47	47,613	-0,613	55	55,300	-0,300	75	75,646	-0,646
5	47	47,117	-0,117	48	48,155	-0,155	58	58,744	-0,744
6	39	36,363	2,637	35	34,675	0,325	47	45,559	1,441
7	53	54,572	-1,572	33	32,057	0,943	53	53,451	-0,451
8	78	78,434	-0,434	100	100,067	-0,067	100	100,416	-0,416
9	90	88,361	1,639	85	84,307	0,693	96	96,367	-0,367
10	83	82,487	0,513	78	77,661	0,339	93	85,127	7,873
11	73	74,393	-1,393	72	71,961	0,039	72	79,543	-7,543
12	55	54,992	0,008	55	54,886	0,114	65	64,090	0,910
13	47	49,298	-2,298	42	42,114	-0,114	52	52,737	-0,737
14	58	56,264	1,736	48	48,922	-0,922	68	67,440	0,560

Insect mortality by contact (IMC), Insect mortality by feeding (IMF), IGR (% Growth Inhibition index)

3.2.2 Molecular Docking

We choose to check those results by using molecular docking to analyze both compounds 6 (The least active compound) and 8 (The most active compound) for their ability to insecticidal activity. The molecular conformations host of the two compounds and the host interaction in the active site with the protein (2ZJU.pdb) are illustrated in Figure 2 and Figure 3. In the binding mode, compounds 6 and 8 are related to the site assets of protein through interactions defeated for the contacts key protein-ligand in the insecticidal activity. And we compared the two compounds the compound 8 is the best activity compared compound 6.

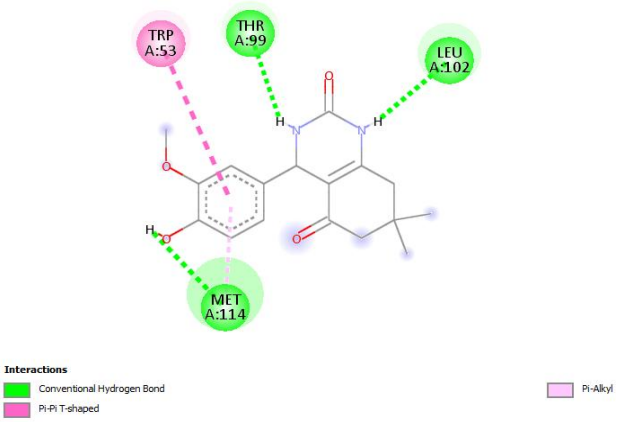


Figure 2: Docking results showing several interactions for compounds 8 with the protein (2ZJU).

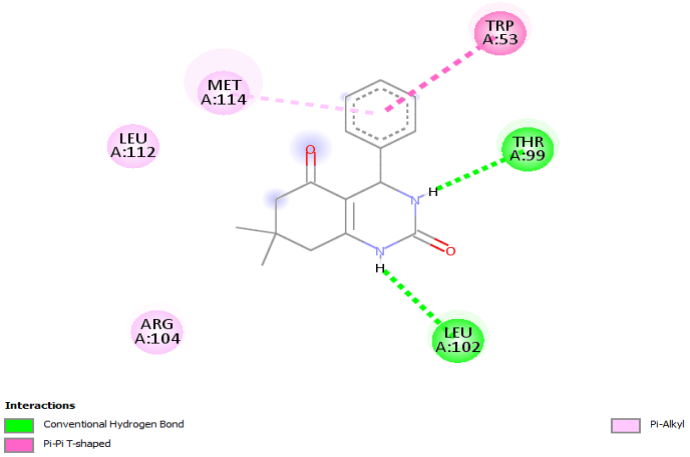


Figure 3: Docking results showing several interactions for compounds 6 with the protein (2ZJU).

The molecular docking results show that the compound 8 is the most active and has the highest insecticidal activity. This result is explained by different interactions: Firstly, the existence of two hydrogen bonds (2.04 Å and 1.89 Å) between the THR99 and LEU102 groups with the hydrogen of the nitrogen atoms of both compounds 8 and 6. Secondly another hydrogen bond between the MET114 group and the hydrogen of hydroxyl group in the compound 8. Finally hydrophobic interaction between the amino acid TRP53 and MET114 with the Pi-system of aromatic ring in the compound 6 and 8. So when comparing the various interactions in the compounds 6 and 8, it is noted that the MET114 causes the two different interactions in the case of compound 8: on one hand an hydrogen bond with the oxygen of the OH group and the other hand an hydrophobic interaction with the aromatic system. This shows the importance of this amino acid and explains the strong insecticidal activity in the case of compound 8.

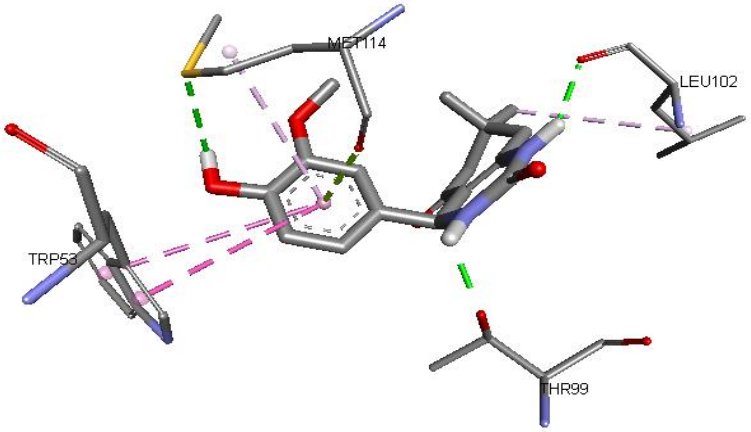


Figure 4: Several interactions in the compounds 8 (Binding energy = -7.27 (Kcal/mol).

4. Conclusion

In this paper quantitative structure-activity relationships are generally used to evaluate and predict the “activity” and other properties of substituted Octahydroquinazolinone. A QSAR study was carried in order to determine a quantitative relationship between structure chemical and biological activity (Insect mortality (contact), Insect mortality (feeding) 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. 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. On the other hand, molecular docking of compounds 6 and 8 with the protein (2ZJU) receptor reveals important interactions (hydrogen bond or hydrophobic interaction) explains the strong insecticidal activity in the case of compound 8.

Acknowledgments

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