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Theoretical Bio-evaluation of 3,5-dimethoxy-N-vinylbenzenamine Analogues as Potential anti-*Sclerotinia sclerotiorum*

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Abstract

Sclerotinia sclerotiorum as a dangerous fungus remains a severe threat to farmers and nation's economy. Fifteen molecular compounds were subjected to quantum chemical study via density functional theory Using Spartan 14 software and the obtained descriptors were used to develop QSAR model using XLSTAT 2020.4.1.1020 and MATLAB.

The predicted IC_{50} using partial least square (PLS) and genetic algorithm (GA) were closer to the observed IC_{50} and the result showed that predicted IC_{50} using GA were more closer to the observed IC_{50} than the predicted IC_{50} using PLS. More so, docking study was observed so as to probe in to molecular interaction between 3,5-dimethoxy-N-vinylbenzenamine derivative and *Sclerotinia sclerotiorum* with PDB ID 2x2s.

Thus, it showed that all the studied compounds have a better ability to inhibit *Sclerotinia sclerotiorum* than carbendazim.

Keywords: *3,5-dimethoxy-N-vinylbenzenamine, Sclerotinia sclerotiorum, QSAR, DFT, Docking*

Introduction

The role of played by plants in the world cannot be overemphasized. It is one of the products produced by nature which human depended on so much for shelter, transportation, medicine and food stuffs etc. [1, 2]. As reported by Rafieian-Kopaei (2012), series of plants like Barberry, Garlic, chamomile, ginger etc are medicinal and they are very useful in treating several diseases like cancer, Diabetes mellitus, viral diseases, fungal disease, hypotension, Jaundice, malaria and fever [3-5].

Fungi are eukaryotic microbes which inhabit various locations like water, food and soil [6-7]. Several factors (moisture, temperature, pH, degree of aeration, quantity and kind of nutrients) which possesses the ability to hinder the growth and distribution of fungi have been reported by many researchers [8]. Most of them are unobtrusive and this could be due to their lesser size as well as their ambiguous existences in soil and on lifeless substance [9].

Therefore, *Sclerotinia sclerotiorum* has been described by scientists as an imperative and disturbing fungus with wide environmental spreading [10]. As reported by Sharma et al., (2015), over 400 species of plants have been infested by *Sclerotinia sclerotiorum* and this has caused colossal damage to economy of many nations [11]. Also, several factors such as temperature and moisture levels etc have been observed to influence the operation of *Sclerotinia sclerotiorum* in the soil. Therefore, understanding of its operation, distribution and its means of survival has assisted scientists in developing anti- *Sclerotinia sclerotiorum* agents [12].

Moreover, the universal use of quantum chemical method via density functional theory in investigating anti-fungal activities of drug-like molecules is still at its highest level [13] and this can be attribute it vastly meaningful part played in explaining the electronic structure and molecular compound's reactivity [14]. Nevertheless, there are other methods in computational chemistry; however the proficient building of innovative measure for explaining and understanding chemical progressions has helped the frequent use of density functional theory method among scientists [15].

Therefore, this work is aimed at identifying molecular descriptors which describe antifungal activities of the studied compounds and to develop QSAR model for predicting biological activity observed compounds as well as observing molecular interaction between 3,5-dimethoxy-N-vinylbenzenamine analogues and *Sclerotinia sclerotiorum*.

Methods

Optimization

Equilibrium geometry of studied 3,5-dimethoxy-N-vinylbenzenamine derivatives were optimized using quantum chemical calculations via density functional theory with 6-31G* as basis set. According to Becke, (1993), three-parameter density functional which comprise of Becke's gradient exchange and the Lee, Yang, Parr correlation functional (i.e. B3LYP) [16]. As reported by Oyebamiji and Semire (2016), selection of basis set for quantum chemical calculation is a function of it precision [17]; thus, 6-31G* basis set was used to optimized the studied compounds. The studied compounds are shown in Table 1.

QSAR Studies

In this work, the obtained molecular descriptors from the optimized studied compounds were used to develop QSAR model (Table 2) so as to predict cytotoxicity of the observed compounds using partial least square methods via XLSTAT 2020.4.1.1020 (32 bit) [18] and genetic algorithm (GA) via MATLAB. The entire selected compounds were divided in two (Training set and test set) and series of arithmetic factors were considered for validation such as adjusted correlation coefficient, Mean Squared Error, P-value, F-value. Also, Absorption, Distribution, Metabolism, Excretion and the Toxicity properties of the studied 3,5-dimethoxy-N-vinylbenzenamine derivatives were done via online software (admetSAR) (http://lmmd.ecust.edu.cn/admetsar1) [19]. The factors considered were Blood Brain Barrier, Caco-2 cell permeability, Human Intestinal Absorption, Ames test. Also, six molecular compounds were proposed and their biological activities were predicted using the developed QSAR model.

Molecular Docking Study

The molecular interaction between 3,5-dimethoxy-N-vinylbenzenamine derivatives and

Sclerotinia sclerotiorum (PDB ID: 2x2s) [20] were investigated using docking study. Series of software (EduPyMOL-v1.7.4.4-Win32, discovery studio 2017, autodock tool 1.5.6 and autodock vina 1.1.2) were used to accomplish this study. The observed grid box was as follows: center (X = 43.197, Y = 9.205, Z = 8.724) and size (X = 56, Y = 40, Z = 40) as well as the spacing was set to be 1.00Å.

Results

Calculated Molecular Descriptors

Series of molecular descriptors obtained from optimization of the studied compounds were reported. The calculated descriptors were highest occupied molecular orbitals energy (E_{HOMO}) (eV), lowest unoccupied molecular orbital energy (E_{LUMO}) (eV), dipole moment (Debye), molecular weight (amu), area (A^2), volume (A^3), polar surface area (PSA) (A^2), Log P, polarizability, hydrogen bond donor, hydrogen bond acceptor (Table 3). The drug-likeness of the studied compounds was observed by considering Lipinski rule of five as reported by Adejoro et al., 2016 [21]. The calculated Lipinski properties were molecular weight (≤500), Lipophilicity (Log P) (≤5), hydrogen bond donor (HBD) (≤5), and hydrogen bond acceptor (HBA) (≤10); thus, this showed that the studied compounds have drug-like properties.

Quantitative Structural Activity Relationship (QSAR) Study

The calculated molecular descriptors obtained from optimization of studied 3,5-dimethoxy-N-vinylbenzenamine were displayed in Table 3 and the correlation between the calculated descriptors were observed and investigated via Pearson correlation matrix. As shown in table 4, reasonable correlation was observed between the calculated molecular descriptors; therefore, dipole moment was fairly correlated with area, volume as well as polar surface area (PSA) by 0.780, 0.774 and 0.599 respectively. Also, Pearson's correlation between molecular weight and area as well as volume is 0.641 and 0.613. As shown in Table 4, Area is fairly correlated to volume and polar surface area (PSA) by 0.996 and 0.726. More so, volume and polar surface area (PSA) are correlated to polar surface area and inhibition concentration (IC_{50}) by 0.674 and -0.505 respectively.

QSAR Model Analysis via Partial Least Square (PLS) and Genetic Algorithm (GA)

Series of molecular descriptors were obtained from the optimized molecular compounds and the selected descriptors which described anti-*Sclerotinia sclerotiorum* activities of 3,5-dimethoxy-N-vinylbenzenamine derivatives were used to develop QSAR model in order to predict the observed cytotoxicity. As shown in Table 5, the studied compounds were divided into two sets (test set and training set) in order to observe the efficiency of the developed model. The correlation between the predicted IC_{50} obtained using PLS and the observed IC_{50} showed the effectiveness of the developed QSAR model which was confirmed by the calculated correlation coefficient (R^2) (0.901) since predictability of QSAR model could be confirmed by correlation coefficient (R^2) ≤ 0.5 [22, 23]. Also, the catholic spread of the residuals on both sides of zero lines in the graph as displayed in figure 1 and figure 2 exposed that the developed QSAR model did not show any comparative imprecision. The predicted IC_{50} using partial least square were closer to the observed IC_{50}, however, the predicted IC_{50} using genetic algorithm (GA) were much closer to the observed IC_{50} than the predicted IC_{50} using PLS which showed the efficiency of genetic algorithm in developing QSAR model and prediction (figure 3). The selected molecular descriptors which described the anti-*Sclerotinia sclerotiorum* of the studied compounds proved to be effective as shown in the developed QSAR model as well as the contribution of each of the descriptor in the model were displayed in Figure 4. Also, the developed QSAR were validated by considering adjusted correlation coefficient (Adj R^2), Mean square error (MSE), F-value and P-value.

Proposed Novel drug-like compounds

Series of drug-like compounds were proposed and these were achieved via addition of suitable derivatives to the studied parent compounds (Table 6). Also, IC_{50} was predicted for individual proposed compound using the developed QSAR model and the predicted IC_{50} were reported in Table 6. As shown in Table 6, the calculated inhibition efficiency for A2 and A3 proved to be more efficiency than the standard used.

Molecular Docking Study

The molecular interaction between the studied compounds and *Sclerotinia sclerotiorum* (PDB ID: 2x2s) were observed via molecular docking study. According to Ritchie *et al.*, 2008, means of identifying drug-like molecule that has the capability to join with a receptor which is a function of calculated scoring describes molecular docking. Also, the degree of the connectivity between the studied 3,5-dimethoxy-N-vinylbenzenamine derivatives and *Sclerotinia sclerotiorum* (PDB ID: 2x2s) could be enhanced by reducing scoring value [24]. Thus, it was observed that the derivatives attached to the parent compound used in this work were efficient and this could be confirmed via the calculated scoring values (Table 7). Also, comparing the binding affinity for the studied ligands to the standard used, it was observed that all the studied compounds have better ability to inhibit than Carbendazim (Standard). The binding affinity for compound 1-15 are -7.2 kcal/mol, -7.6 kcal/mol, -6.9 kcal/mol, -7.0 kcal/mol, -6.8 kcal/mol, -7.0 kcal/mol, -6.8 kcal/mol, -6.8 kcal/mol, -6.9 kcal/mol, -7.2 kcal/mol, -7.3 kcal/mol, -7.0 kcal/mol, -7.0 kcal/mol, -7.0 kcal/mol, -7.9 kcal/mol. The residues involved in the interaction between each ligand and the receptor as well as the type of non-bonding interaction was reported in Table 7.

Discussion

Cytotoxity of fifteen (15) molecular compounds were studied using quantum chemical method, QSAR and docking studies. The obtained descriptors described well the anti- *Sclerotinia sclerotiorum* activity of 3,5-dimethoxy-N-vinylbenzenamine derivatives and the obtained descriptors were further used to develop QSAR model. The developed model proved to be efficient via its predicting strength; however, genetic algorithm proved to be more predictive than PLS. Also, docking study reveals the molecular interaction between the studied ligands and the receptor; therefore, the result showed that all the studied compounds have better ability to inhibit *Sclerotinia sclerotiorum* than the standard.

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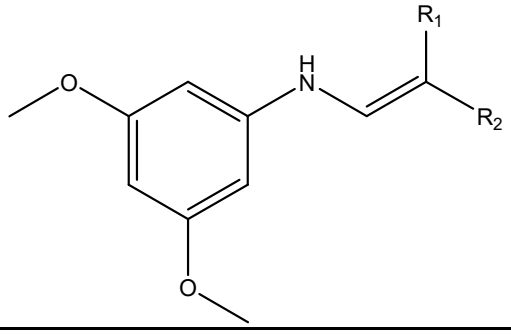
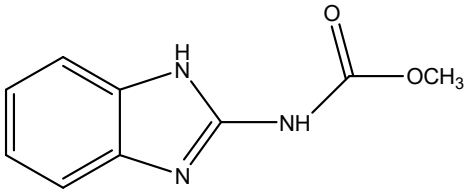
Table 1: Schematic structure of selected studied compounds



	R_1	R_2
1	Ph	Ph
2	4-tBu-Ph	4-NO_2-Ph
3*	CH_3	2-CH3-Ph
4	3,4-2Cl-Ph	3-Py
5	4-CH_3-Ph	4-Py
6	3,4-2CH_3-Ph	4-Py
7*	2-CH_3-3-Cl-Ph	4-Py
8	4-Br-Ph	4-Py
9	4-Br-Ph	2-Cl-3-Py
10	4-CH_3-Ph	2-Cl-3-Py
11*	3,4-2CH_3-Ph	2-Cl-3-Py
12	4-CH_3-Ph	3-Cl-4-Py
13	3,4-2CH_3-Ph	3-Cl-4-Py
14*	4-Br-Ph	3-Cl-4-Py
15	4-Ph-Ph	3-Cl-4-Py
Carbendazim		

**** denote test set***

Table 2: Calculated QSAR model for the observed 3,5-dimethoxy-N-vinylbenzenamine derivatives

Equation	F	P-value	R^2	Adjusted R^2	MSE
IC_{50} = -624.32 - 6.24(DM) - 1.035(MW) + 23.36(AREA) - 21.13(VOL) - 8.52(PSA)	9.062	P < 0.0001	0.901	0.801	69.683

Table 3: Calculated descriptors for 3,5-dimethoxy-N-vinylbenzenamine derivatives

	E_{HOMO}	E_{LUMO}	DM	MW	AREA	VOL	PSA	LOG P	POL	HBD	HBA
1	**-5.39**	-0.82	2.4	333.391	377.09	353.34	35.52	4.81	68.96	0	4
2	-5.56	-2.67	10.35	434.496	482.19	448.49	74.827	6.58	77.07	0	7
3	-5.47	-0.46	2.32	285.347	334.81	305.7	36.285	4.11	64.99	0	4
4	-5.67	-1.06	7.15	437.714	416.56	387.62	44.368	4.87	71.73	0	5
5	-5.54	-1.12	7.04	348.406	390.99	364.75	43.851	2.57	69.92	0	5
6	-5.58	-1.15	7.44	376.46	423.82	400.16	44.042	2.92	72.79	0	5
7	-5.65	-1.17	3.11	382.851	404.30	378.2	43.288	4.24	70.99	0	5
8	-5.60	-1.15	2.76	413.275	392.40	364.88	43.025	4.02	69.92	0	5
9	-5.65	-1.08	4.42	447.72	407.64	378.53	43.018	4.67	71.00	0	5
10	-5.57	-1.03	5.99	382.851	406.08	378.40	43.820	3.41	71.00	0	5
11	-5.55	-1.04	6.37	410.905	435.94	413.71	43.518	3.57	73.87	0	5
12	-5.63	-1.29	8.79	382.851	406.48	378.14	43.892	3.22	71.02	0	5
13	-5.67	-1.33	9.09	410.905	439.31	413.56	44.075	3.57	73.90	0	5
14	-5.71	-1.33	8.36	447.720	406.83	378.02	43.906	3.18	71.00	0	5
15	-5.64	-1.30	8.58	444.922	467.99	443.79	43.883	4.41	76.35	0	5

Table 4: Pearson's correlation matrix for selected molecular descriptors

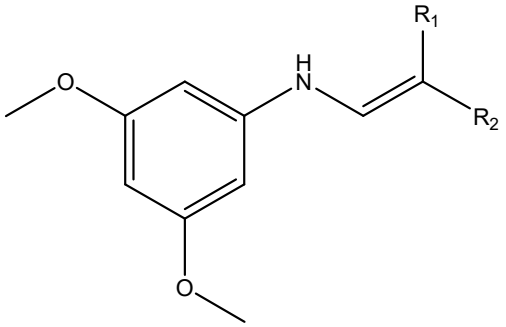
	DM	MW	AREA	VOL	PSA	IC_{50}
DM	**1.000**					
MW	0.313	**1.000**				
AREA	0.780	0.641	**1.000**			
VOL	0.774	0.613	0.996	**1.000**		
PSA	0.599	0.401	0.726	0.674	**1.000**	
IC_{50}	-0.203	-0.140	-0.320	-0.311	-0.505	**1.000**

Table 5: Experimental and Calculated Inhibition concentration

	Observed IC_{50}	PLR	GA
1	52.450	56.631	52.41845
2	11.340	12.141	11.3253
3*	100.00	119.213	99.98545
4	33.220	41.326	33.20545
5	25.760	24.752	25.74719
6	10.970	10.370	10.95719
7*	27.95	45.170	27.9441
8	25.760	21.517	25.7551
9	43.960	43.181	43.95712
10	60.940	60.027	60.93774
11*	68.60	-17.312	68.59793
12	65.890	56.781	65.88793
13	32.310	42.880	32.30836
14*	53.20	2.87	53.19847
15	50.770	43.765	50.76847
Carbendazim	0.45	-	-

**denote Test set*

Table 6: Proposed drug-like compounds and predicted IC_{50}



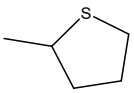
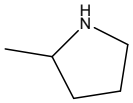
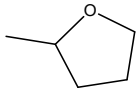
	R_1	R_2	IC_{50}
A1	OCH_3		46.07
A2	OCH_3		-9.79
A3	OCH_3		-6.10
A4	CH_2F	C_2H_5	141.54
A5	CHF_2	C_2H_5	122.47

Table 7: Scoring and residues involved in the interaction between the studied complexes

	Scoring (kcal/mol)	Residues involved in the interactions	Types of Non-bonding interaction involved
1	-7.2	ALA-140, LYS-100, SER-117	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Sigma, Pi-Alkyl
2	-7.6	LYS-100, ALA-140, SER-139	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavourable Donor-Donor, Pi-Cation, Alkyl, Pi-Akyl
3	-6.9	TRP-24, TYR-37, SER-44, THR-38	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Sigma, Pi-Pi- Stacked, Pi-Pi T-shaped, Pi-Alkyl
4	-7.0	ALA-140, LYS-100, ASN-114	Conventional Hydrogen Bond, Pi-Cation, Pi-Alkyl, Alkyl
5	-6.8	ALA-140, LYS-100, SER-117	Conventional Hydrogen Bond, Unfavourable Acceptor-Acceptor, Pi-Cation, Pi-Alkyl, Alkyl
6	-7.0	ALA-140, GLN-121, LYS-100, ASN-113	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Sigma, Pi-Alkyl
7	-6.8	ALA—140, LYS-100, ASN-113, PRO-101	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Sigma, Pi-Alkyl
8	-6.8	LYS-100, GLN-121, ALA-140	Conventional Hydrogen Bond, Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Sigma, Pi-Alkyl
9	-6.9	LYS-100, ALA-140, GLY-120, PRO-101	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Alkyl, Alkyl
10	-7.2	GLY-120, ALA-140, LYS-100	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Alkyl, Alkyl
11	-7.3	GLY-120, ALA-140, LYS-100	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Alkyl, Pi-Alkyl
12	-7.0	TYR-37, GLY-40, ALA-47, PRO-43, SER-44, TRP-24	Conventional Hydrogen Bond, Pi-Pi stacked, Pi-Pi T-shaped, Alkyl, Pi-Alkyl
13	-7.0	ALA-140, LYS-100	Conventional Hydrogen Bond, Unfavourable Donor-Donor, Pi-Cation, Alkyl, Pi-Alkyl

14	-7.0	ASN-46, TRP-24, TYR-37, ARG-35	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Pi Stacked, Pi-Pi T-shaped, Alkyl
15	**-7.9**	LYS-100, ALA-140, GLN-121	Carbon Hydrogen Bond, Pi-Cation, Pi-Alkyl
Carbendazim	-6.1	VAL-6, LEU-53, GLY-58, TYR-107, TYR-63, ALA-61	Conventional Hydrogen Bond, Pi-Pi T-shaped, Pi-Alkyl

Figure 1: Standardized residual against observed IC_{50}

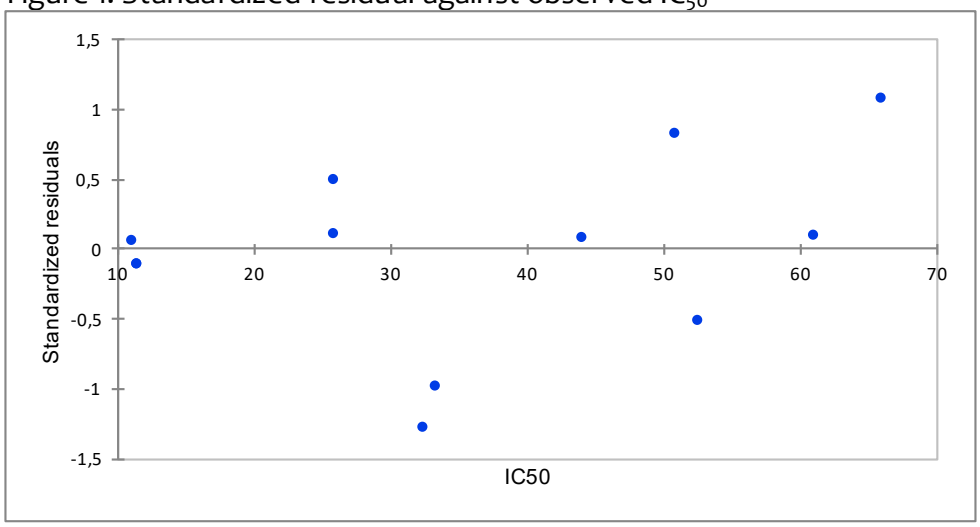


Figure 2: Standardized residual against predicted IC_{50}

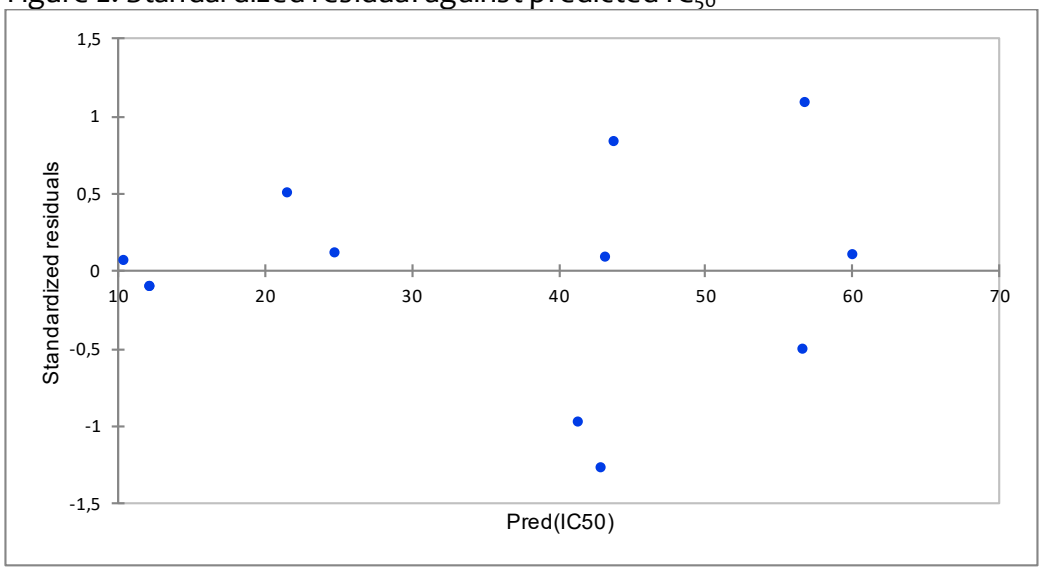


Figure 3: Calculated predicted IC_{50} against experimental IC_{50} via PLS

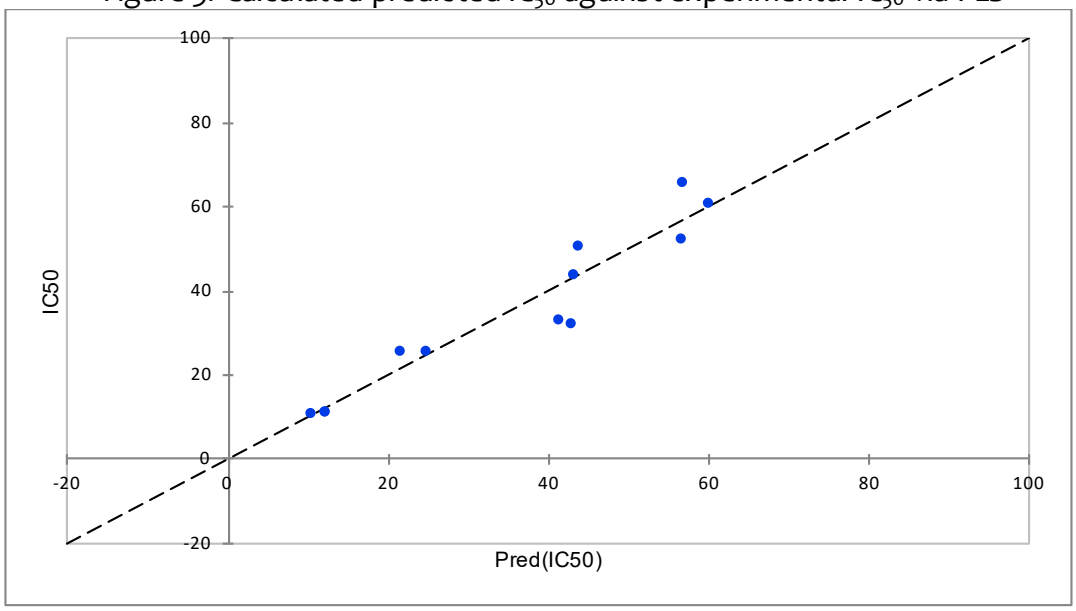


Figure 4: Graph of standardized coefficient against the variable

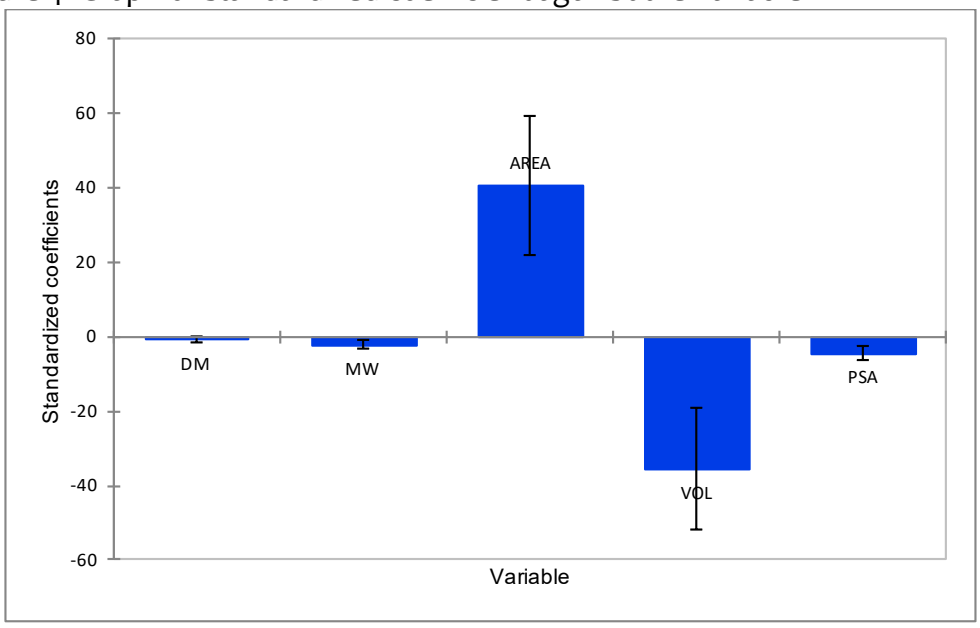
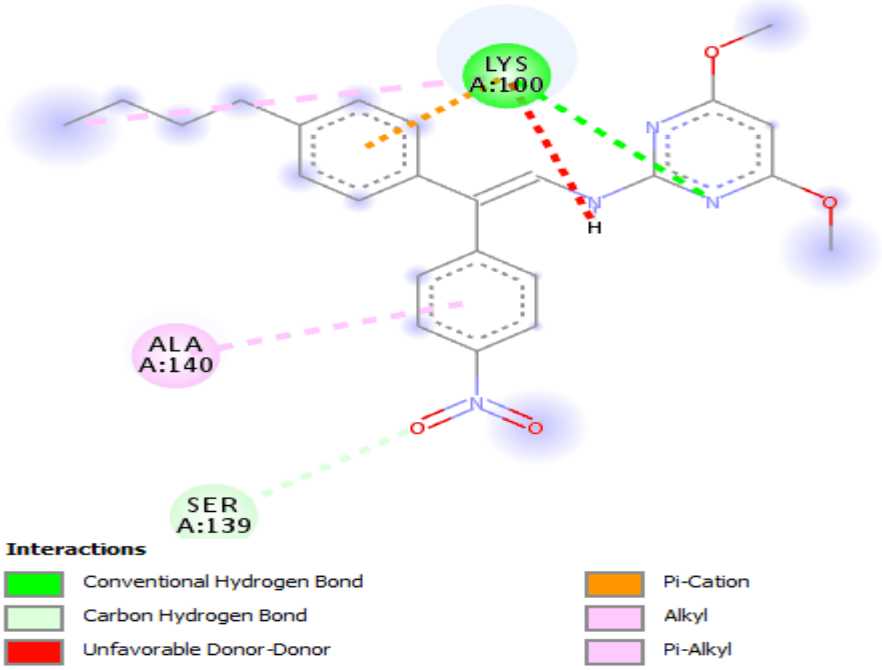
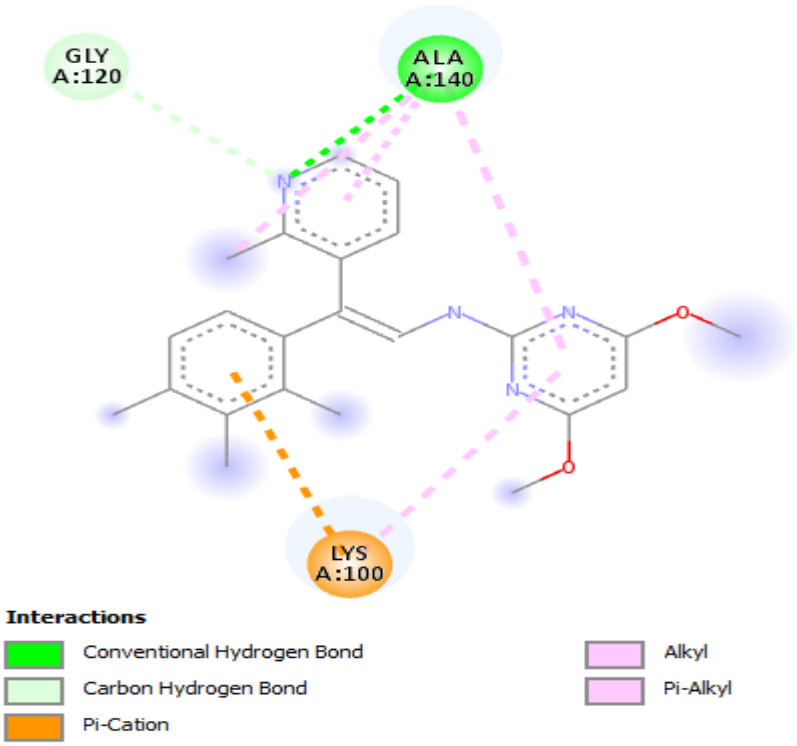
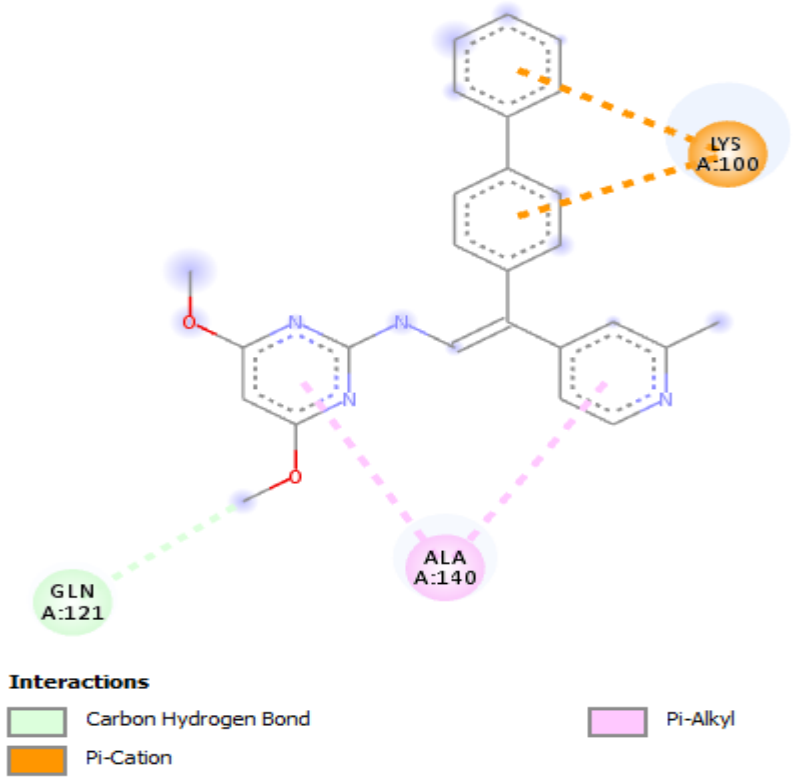


Figure 5: Structure of the interactions between compounds 2, 11, 15 and *Sclerotinia sclerotiorum* (PDB ID: 2x2s) respectively






LYS
A:100
GLN
A:121
ALA
A:140
Interactions
Carbon Hydrogen Bond
Pi-Cation
Pi-Alkyl