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DFT, QSAR AND DOCKING STUDIES ON 2-[5-(ARYLOXYMETHYL)-1, 3, 4-OXADIAZOL-2-YLSULFANYL] ACETIC ACIDS DERIVATIVES AGAINST *E. COLI*.

Oyebamiji Abel Kolawole[1] and Adeleke Babatunde Benjamin[2*]

[1]Department of Pure and Applied Chemistry, Ladoke Akintola, University of Technology, P.M.B. 4000, Ogbomoso, Oyo State, Nigeria.
[2]Department of Chemistry, University of Ibadan, Ibadan, Nigeria.

ABSTRACT: *The growing occurrence of multi-drug resistant bacteria contagions has encouraged the pursuit for fresh and active antibacterial drugs. The derivatives of acetic acid play a crucial role in several manufacturing companies like, chemicals companies, plastics industries, drug production companies etc. Also, the anti-E-coli activity of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids derivatives were observed by using density functional theory (DFT), Quantitative Structure Activity Relation (QSAR) and docking methods. The calculated descriptors were used to develop QSAR model which reproduced the experimental inhibition concentration (IC_{50}) by using equation 3. More so, compound 3f showed a greater inhibiting ability than other compounds when docked against E. coli cell line (1grx).*

KEYWORDS: 2-[5-(Aryloxymethyl)-1, 3, 4-Oxadiazol-2-Ylsulfanyl] Acetic Acids Derivatives, *E. Coli*, DFT, QSAR, Docking.

INTRODUCTION

Globally, contagious bacterial diseases remain a serious challenge. It excessive widespread is a function of the frequent use of antibacterial agents and this could breeds bacteria with ability to resist commonly used antibiotics [1]. The deficiency of effective drug that inhibit bacteria has pushed scientist to develop new set drug in combatting diseases that originated from bacteria species [2-5].

Bacteria and their phages is one of the plenteous and primogenital organisms found in the universe. They exist among human being and this is a function of its importance to human being [6-9]. They are very tiny in nature to see with human eye unless assisted with lenses. Bacteria are very important for apposite development, sustenance, and resistance to difficulty. [10-11].

The synthesis of acetic acid by isolation through refinement of vinegar was achieved many years ago [12]. The idiosyncratic scent and sharp taste of vinegar brings about several properties in its pure state [13-15]. The use of acetic acid is its highest level in several industries like, chemicals companies, in the production of antibiotics, plastics industries etc. [16-17].

Moreover, most of the desire of scientists in studying quantitative structure activity relationships (QSAR) is majorly to probe into interactions that exist between the biological activities of molecules and their chemical structures. Over the years, QSAR has been very useful in commercial drug transposition and in predicting the interaction between drug-drug

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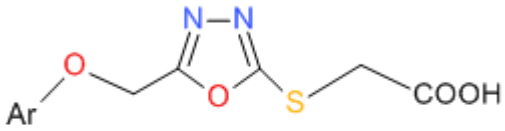
relationships [18-23]. Also, QSAR as a mathematics model offer help in the case of classic chemicals [24-25].

Furthermore, the study of molecular docking helps to observe the interaction between drug-like molecules and a particular receptor based on the calculated binding energy [26]. This method basically combines algorithms such as Monte Carlo stimulation, molecular dynamics and fragment based search methods [27]. Hence docking plays a very serious part in the normal drug design.

Thus, a set of seven compounds (Figure 1) which were already synthesized and it anti- *E. coli* activities were observed by Neelam *et al*, (2016) were optimized with the use of density functional theory method [28]. These studied compounds are: 2-(5-(phenoxymethyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **(ES1),** 2-(5-((4-methylphenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) acetic acid **(ES2),** 2-(5-((4-methoxyphenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) acetic acid (**ES3**), 2-(5-((4-chlorophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **(ES4),** 2-(5-((4-bromophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **(ES5),** 2-(5-((4-fluorophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **(ES6)** and 2-(5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **(ES7)**. Hence, this worked is aimed at calculating molecular descriptors using density functional theory method and then develop a quantitative structure activities relationship model so as to investigate the biological activities of the selected molecular compounds. Also, the optimized compound were docked against the enzyme (1grx) in order to calculate free binding energy.



Ar	
3a	C_6H_5
3b	CH_3-C_6H_4
3c	CH_3O-C_6H_4
3d	Cl-C_6H_4
3e	Br-C_6H_4
3f	F-C6H4
3g	NO_2-C_6H_4

Figure 1: The schematic view of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids Derivatives

Computational Details

The use of quantum chemical method through density functional theory for the optimization of seven molecular compounds were performed. This optimization was done with the use of 6-31(d,p) basis set and the obtained molecular descriptors which describe the cytotoxicity were used to develop QSAR model. Quantum chemical software like Spartan '14 by wavefunction Inc (Spartan 14) was used in this work.

Furthermore, QSAR study reveal the quality of a built model which helps to probe into biological activity of compounds via its predictability as well as its fitting [29]. The problem encountered in QSAR studies is selecting descriptors which have high predictability for modeling [30]. In this work, the most useful molecular parameters are chosen from other calculated descriptors through linear multiple regression using Gretl 1.9.8. The validation of

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QSAR could now be achieved by using some statistical analysis such as cross validation (R^2) and adjusted R^2 (Equation 1 and 2).

$$CV.R^2 = 1 - \frac{\sum(Y_{obs} - Y_{cal})^2}{\sum(Y_{obs} - \bar{Y}_{obs})^2} \text{----------(1)}$$

The adjusted R_2 adjusted could be calculated using equation (2)

$$R_a^2 = \frac{(N-I)\times R^2 - P}{N-1-P} \text{----------(2)}$$

Molecular Docking

Docking studies was accomplished by using docking software (Discovery studio 4.1, AutoDock Tool 1.5.6 software, AutoDock vina 1.1.2 and Edu pymol version 1.7.4.4 [31-37].

The optimized compounds were docked to three dimensional structure of ***E. coli*** cell line with PDB ID "1grx". The receptor were docked with the use of Lamarckian genetic algorithm in the gouge of the receptor with the grid dimension 28 × 28 ×26 Å (grid size).

RESULT AND DISCUSSION

Geometries

The schematic structure of the studied compounds and the optimized structure which were gotten by B3LYP/6-31G(d,p) were shown in figure 1 and 2 respectively. The effect of the substituents (Ar = C_6H_5, CH_3-C_6H_4, CH_3O-C_6H_4, Cl-C_6H_4, Br-C_6H_4, F-C_6H_4 and NO_2-C_6H_4) attached have profound effect on the geometries of the main compound i.e. C4-O2 and O2-C3 were affected while C3-O1, O1-C5, C5-S1 almost have the same value when the substituent were changed for all the compound (Table 1). This connotes that, the substituent attached has little or no effect on C3-O1, O1-C5, C5-S1in the studied compounds. For the bond angle and dihedral angle, the same trend was observed. Also, it was observed that all the studied molecules were planar according to the calculated dihedral angle and this shows that the presence of the attached molecules enhanced their chemical reactivity.

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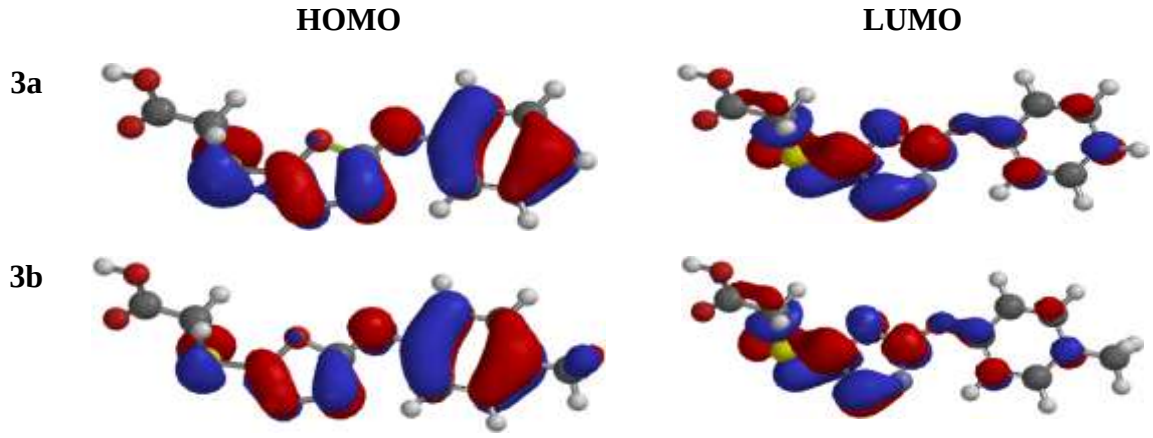
Table-1: Selected geometry descriptors obtained by B3LYP/6-31G(d,p) for 3a-3g

	3a	3b	3c	3d	3e	3f	3g
C4-O2	1.403 Å	1.404 Å	1.405 Å	1.399 Å	1.399 Å	1.402 Å	1.402 Å
O2-C3	1.322 Å	1.321 Å	1.320 Å	1.324 Å	1.324 Å	1.322 Å	1.322 Å
C3-O1	1.357 Å	1.357 Å	1.357 Å	1.356 Å	1.355 Å	1.356 Å	1.356 Å
O1-C5	1.382 Å	1.382 Å	1.382 Å	1.382 Å	1.383 Å	1.382 Å	1.382 Å
C5-S1	1.751 Å	1.752 Å	1.752 Å	1.751 Å	1.751 Å	1.751 Å	1.751 Å
C4,O2,C3	124.56 °	124.44 °	124.31 °	124.38 °	124.35 °	124.36 °	124.38 °
O2,C3,O1	113.27 °	113.33 °	113.41 °	113.24 °	113.30 °	113.30 °	113.33 °
C3,O1,C5	101.60 °	101.62 °	101.63 °	101.55 °	101.55 °	101.58 °	101.59 °
O1,C5,S1	119.95 °	119.92 °	119.82 °	119.95 °	119.96 °	119.92 °	119.91 °
C4,O2,C3,O1	178.42°	179.46 °	177.86 °	179.50 °	178.60 °	-179.91 °	178.30 °
O2,C3,O1,C5	-178.81 °	-178.84 °	-178.87 °	-178.60 °	-178.68 °	-178.62 °	-178.90 °
C3,O1,C5,S1	-174.89 °	-175.04 °	-175.30 °	-174.75 °	-174.69 °	-174.81 °	-175.05 °

Electronic Descriptors

In this work, several descriptors were obtained which depicted the anti-*E-coli* activities of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids such as highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), dipole moments, energy band-gap, lipophilicity (Log P). The highest occupied molecular orbital energy which reveal the ability of molecules to give electron to other compounds in the surroundings provide equitable information about the excitation features of molecules [38-40]. Likewise, E_{LUMO} depict the capacity of a molecule to accept electron from the neighboring compounds with ability to release it. Thus, there were no correlation between E_{HOMO} and the IC_{50} as well as E_{LUMO} and IC_{50} as shown in Table 1. The HOMO-LUMO overlay were displayed in Figure 2. More so, the calculated band gap are 5.61eV, 5.48eV, 5.16eV, 5.53eV, 5.49eV, 5.54eV, 5.25eV for **3a-3g.** As shown in Table 1, the band-gap calculated in this work show no correlation with the inhibition concetration.



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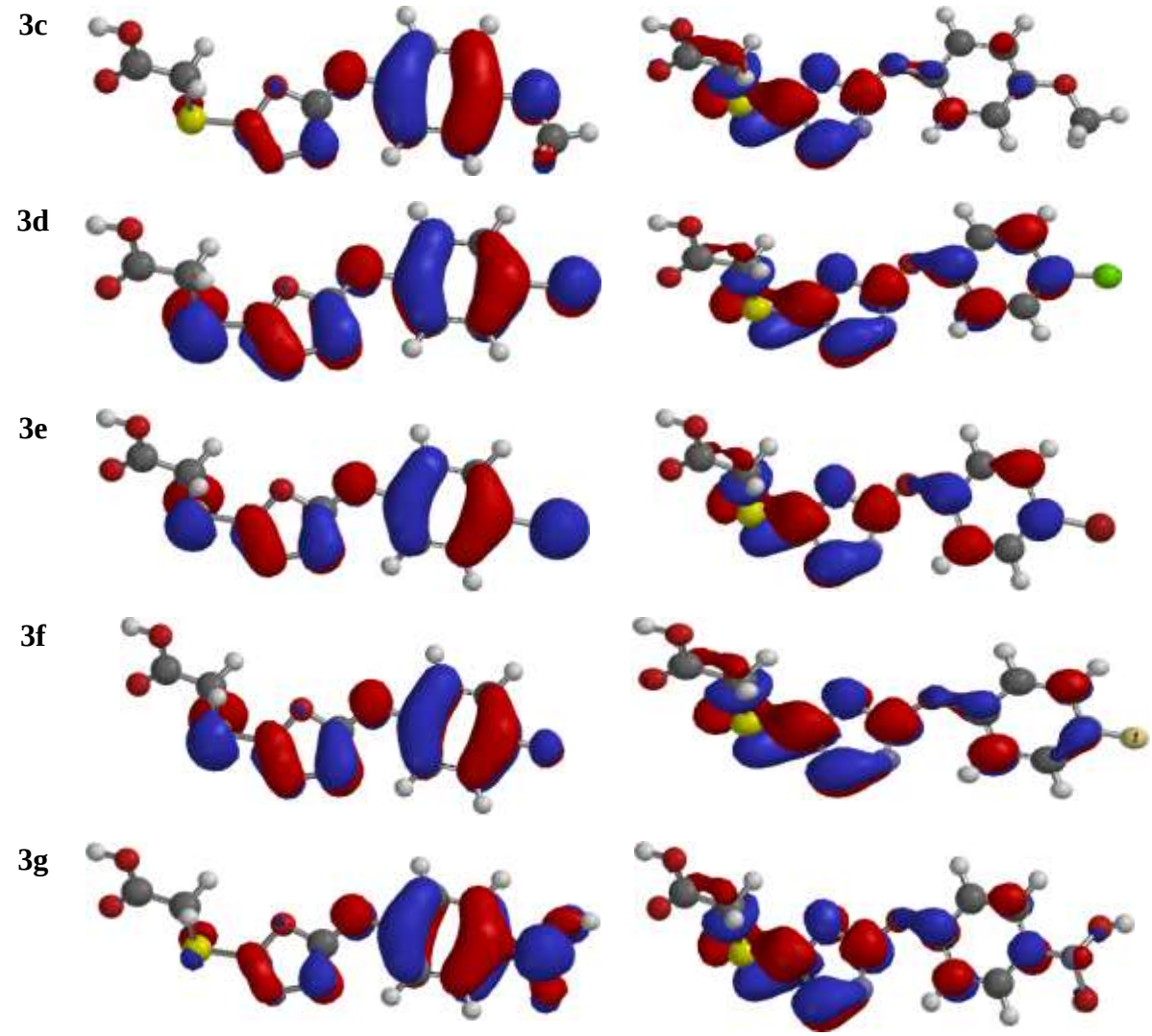

Figure 2: HOMO-LUMO overlay of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids derivatives.

Moreover, increased solvation energy could contribute to the drug resistance; thus, **3c** and **3g** were better in term of solvation energy. Also, irregular property of diverse drug-like molecule is due to large value of dipole moment [41], so, **3a-3g** are suitable in term dipole moment, meanwhile the calculated dipole moment values are moderate. For polar surface area (PSA), all the calculated drug-like molecule are orally potent since it is observe from report that polar surface area value should not exceed $120A^2$ for drug molecules that are orally active [42,43]. Ovality as a degree of how the structure of a molecular compound approaches a shape [44] was calculated to be 1.41, 1.44, 1.46, 1.44, 1.44, 1.42, and 1.48. According to Adejoro et al., 2014, the higher the value of ovality, the tendency of a molecular compound to deviate from its shape; thus, the molecule loses it activity [45]. So, in this work, the studied compounds are active in term of ovality. Also, there is fair correlation between the ovality and inhibition concentration.

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Table 1: The calculated molecular descriptors obtained from the studied compounds

	HOMO	LUMO	BG	DM (Debye)	SE (Kj/mol)	LOGP	OVALITY	PSA	HET	POL	HBA	HBD	E. coli (MTCC 40)
3a	-6.46	-0.85	5.61	4.54	-48.49	3.20	1.41	68.15	-1.054	58.09	6	1	0.55
3b	-6.30	-0.82	5.48	4.67	-47.41	3.69	1.44	68.19	-1.054	59.60	6	1	0.50
3c	-5.94	-0.78	5.16	3.90	-52.66	3.07	1.46	75.14	-1.058	60.40	7	1	0.50
3d	-6.52	-0.99	5.53	4.71	-46.76	3.76	1.44	68.00	-1.059	59.22	6	1	0.40
3e	-6.52	-1.03	5.49	4.65	-48.21	4.03	1.44	68.07	-1.055	59.59	6	1	0.40
3f	-6.44	-0.90	5.54	4.57	-42.20	3.36	1.42	68.04	-1.061	58.48	6	1	0.35
3g	-6.14	-0.89	5.25	4.68	-55.09	2.84	1.48	116.63	-1.056	60.43	9	3	0.30

QSAR Studies

Quantitative structure activity relationship (QSAR) provides an atmosphere to predict the activity of various molecular compounds and it also explain the chemo-biological interactions [46, 47]. Also, it reveal the relationship between cytotoxicity and molecular descriptors [48, 49]. Therefore, descriptors obtained from seven calculated molecules together with experimental inhibitory concentration (IC_{50}) were used in building QSAR model by using multiple linear regression. Thus, the developed QSAR model reproduced the experimental IC_{50} using equation 3 as shown in Table 2.

IC_{50} = -2.29308 -0.0229752(SE) -0.116935(HBD) -0.414575(HOMO) + 0.974503(LUMO)----------**(3)**

Table 2: Stepwise regression result for anti-bacteria activity

COMP	OBSERVED	PREDICTED	RESIDUAL
3a	0.55	0.55	-0.00
3b	0.50	0.49	0.01
3c	0.50	0.50	-0.00
3d	0.40	0.40	-0.00
3e	0.40	0.40	0.00
3f	0.35	0.35	-0.00
3g	0.30	0.30	0.00

Four descriptors were selected out of many descriptors generated using Gretl software and these were observed to depict anti-*E-coli* activity. Furthermore, the efficiency of the developed QSAR model could not be totally relied on by using R^2only, therefore, validation and estimation of the developed QSAR model is necessary by observing the following statistical measures: cross validation CV.R^2 and Adjusted R^2 (R_a^2) as shown in Table 3.

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Table 3: Statistical parameters for validation of QSAR model

N	p	R^2	CV.R^2	R^2_{adj}	F
7	4	0.997	0.996	0.993	0.004

The calculated CV.R^2 is 0.996 and the calculated R_a^2 is 0.993. According to Marrero et al., 2004, developed QSAR model is valid and it is dependable when the CV.R^2 is greater than 0.5 (standard) and the R_a^2 is greater than 0.6[48]. Therefore, in this work, the developed model is proved to be dependable and appropriate according to the calculated geometric measures (Table 2).

Docking Studies

The means of identifying ligands that have the ability to interrelate with a receptor is a function of free binding energy. Ritchie *et al*., 2008 reported that lowering of free binding energy enhances impulsiveness of binding interaction which occur between drug-like molecules and the receptor [49]. Thus, compound 3f proved to inhibit 1grx (receptor) than other docked compounds against the receptor as shown in Table 4 and the stable conformation of compound 3f inside the active site of 1grx was displayed in figure 3. It was observed that the lower binding energy observed for compound 3f is a function of fluorobenzene attached to 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids.

Table 4: Interactions between ligands and 1grx receptor

comp	Affinity (kcal/mol)	H-Bond Between protein residues in the binding pocket and Drug	Distance
3a	-5.3	(i) THR-73, LIG: N (ii) ASP-74, LIG:O (iii) ASP-74, LIG:O (iv) GLY-71, LIG:H (v) THR-58, LIG: O	(i) 2.5 (ii) 3.3 (iii) 2.9 (iv) 2.7 (v) 2.7
3b	-5.2	(i)LYS-51, LIG: O (ii) LYS-51, LIG:O (iii) HIS-68, LIG:O	(i)2.4, (ii) 2.8, (iii) 2.0
3c	-5.1	(i) LYS-54, LIG: O (ii) GLU-57, LIG:O (iii) THR-58, LIG:O (iv) THR-73, LIG:N	(i) 2.3 (ii) 2.0 (iii) 2.2 (iv) 2.4
3d	-5.3	(i) LYS-54, LIG:O (ii) PRO-55, LIG:O (iii) GLU-57, LIG:O (iv) THR-58, LIG:O (v) THR-73, LIG: N	(i) 2.3 (ii) 3.3 (iii) 2.1 (iv) 2.3 (v) 2.6
3e	-5.2	(i) ASP-74, LIG:N (ii) ASP-74, LIG:N (iii) PRO-55, LIG:O (iv) GLU-57, LIG: O (v) THR-58, LIG:O	(i) 3.5 (ii) 3.3 (iii) 2.9 (iv) 1.9, (v) 2.0
3f	-5.5	(i) LYS-11, LIG: O (ii) GLU-57, LIG:O (iii) THR-58, LIG:O (iv) ASP-74, LIG:N	(i) 2.4, (ii) 1.9 (iii) 2.2, (iv) 3.3
3g	-5.4	(i) TYR-35, LIG: N (ii) TYR-33, LIG:N (iii) TYR-33, LIG:O (iv) GLU-22, LIG: O (v) LYS-18, LIG: O (vi) ARG-8, LIG: O (vii) ARG-8, LIG: O	(i) 2.4,(ii) 3.3, (iii) 2.7, (iv) 2.9, (v) 2.1, (vi) 2.2 (vii) 2.0

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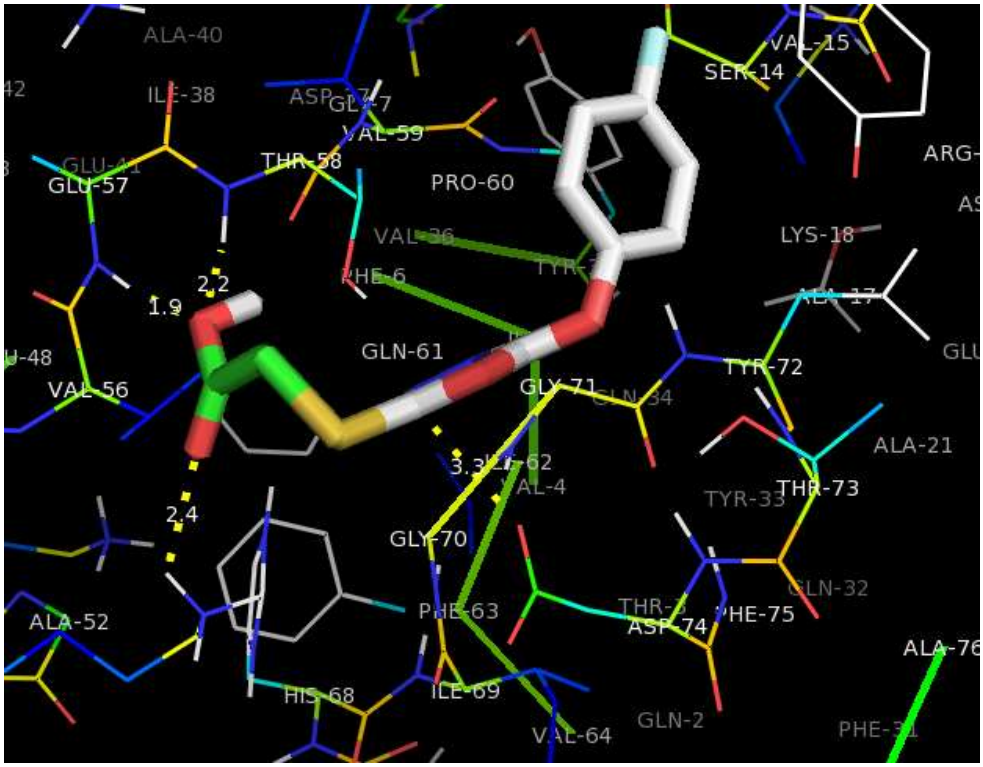

Figure 3: Binding interaction of 3f with 1grx.

CONCLUSION

The biological activity of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids derivatives were observed by considering the geometry and the electronic descriptors using density functional theory method. The developed QSAR model reproduced the observed inhibition concentration via equation 3 and the results obtained from docking study predicted steady structures of the drug-like molecules inside the active site of the enzyme. Also, compound 3f inhibited 1grx more than other studied compounds.

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