



RESEARCH PAPER

STUDIES OF 2-[5-(ARYLOXYMETHYL)-1, 3, 4-OXADIAZOL-2-YLSULFANYL] ACETIC ACID DERIVATIVES FOR ANTI-BACTERIAL ACTIVITIES VIA DFT, QSAR AND DOCKING APPROACHES

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The inhibitory activity of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acid derivatives were considered and used against *S. aureus* cell line using density functional theory (DFT), quantitative structure activity relationship (QSAR) and docking methods. In this paper, many parameters (HOMO, LUMO, Log P, Molecular weight, dipole moment, chemical hardness, chemical potential and solvation energy) obtained via DFT method disclosed that each parameters obtained has a balanced connection with experimental anti-bacterial activity. Moreover, the predicted bioactivity (IC₅₀) agreed well with the observed IC₅₀ using the developed QSAR model. More so, the studied compounds were docked against *S. aureus* cell line (4b19) and the binding energy obtained from ligand-receptor.

Key words: Oxadiazole analogs, Acetic acid derivatives, DFT, QSAR, Molecular docking.

INTRODUCTION

One of the primogenital and most copious being formed in the globe is bacteria and their phages. They are advantageous for well-being of human; therefore, they live together with human being (Backhed *et al* 2005; Fauci *et al* 2005; Kaiser, 2005). Bacteria are very insignificant to be hold with the unassisted eye and are categorized by prokaryotic cellular organization. More so, the presence of bacteria in the body is much more than normal human-cells, thus, they are necessary for apt improvement, sustenance, and opposition to malady (Maloy and Schaechter, 2006; Overbye and Barrett, 2005).

Acetic acid is the molecular compound with uniqueness aroma and acerbic taste of vinegar. Several derivatives of acetic acid are very useful in the production of industrial chemicals,

pharmaceuticals (NSAIDS), perfumes, plastics, synthetic fibers, explosives, antifungals and weed killers (Brogden, 1986; Dahiya and Kaur, 2007; Dahiya and Mourya, 2012; Dahiya *et al* 2006a; 2006b; 2008).

Furthermore, the global use of density functional theory in the study of molecular compounds with anti-bacterial activities by scientists is at its highest level (Oyebamiji and Semire, 2016a). This is due to it highly momentous role played in explicating the electronic structure and reactivity of compounds (Kraka and Cremer, 2000). However, computational chemistry comprise of other methods, but the efficient building of new measure for justifying, predicting and understanding chemical processes made density functional theory stand out technique (Jacquemin *et al* 2009). Now,

quantum chemical calculation *via* density functional theory helped to recognize the antibacterial activities of descriptors by linking the observed facts to calculated molecular descriptors like HOMO energy, LUMO energy, band gap energy, dipole moment, charges on every heteroatoms etc. (Hansch, 1969; Ramsden, 1990).

Quantitative Structural Activity Relationship (QSAR) as an algebraic model that embroils the association between physicochemical descriptors of a ligand to its biological doings (Oyebamiji and Semire, 2016b). In bulk system, toxicity of substance is predicted with the aid of quantitative structural activity relationship and also helps in the case of classic chemicals (Dahl *et al* 2014; Oyebamiji and Semire, 2016c). The use of calculated molecular parameters obtained from quantum chemical methods (QCM) for building QSAR models has been described to be adequate for generating ample QSAR. Therefore,

the use of quantum chemical descriptors has great importance (Arulmozhiraja and Morita, 2004; Gu *et al* 2009; Eroglu and Turkmen, 2007; Zhu *et al* 2010).

In molecular biology and computer-based drug device, docking as an emergent device is essential (Sharma *et al* 2011; Balasubramanian and Vijaya Gopal, 2012; Sharma and Kumar, 2014). It can also be used to do practical selection on vast set of molecules and scoring as well as divulging the steps involved in prevention of target binding site by ligands. Therefore, the calculations of interaction energy can be shown in form of "dock score" (Morris and Lim-Wilby, 2008).

Therefore, in present study, seven compounds (**Figure 1**) synthesized and screened against *S. aureus*, were optimized *via* density functional theory method so as to obtain molecular descriptors and used by calculating virtual screening and binding energy (Jain *et al* 2016).

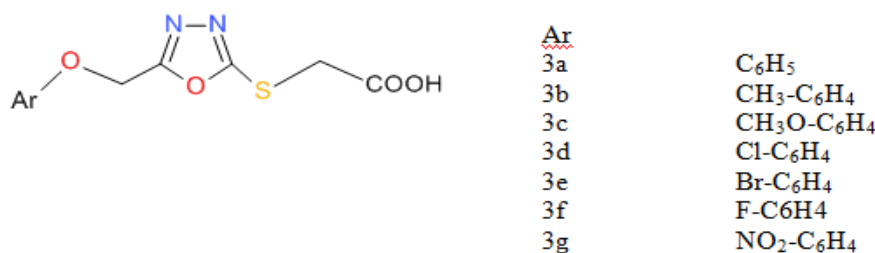


Fig. 1. The schematic structures of the 2-[5-(aryloxymethyl)-1,3,4-oxadiazol-2-ylsulfanyl] acetic acids derivatives

These compounds include 2-(5-(phenoxy-methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3a**, 2-(5-((4-methylphenoxy) methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3b**, 2-(5-((4-methoxyphenoxy) methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3c**, 2-(5-((4-chlorophenoxy) methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3d**, 2-(5-((4-bromophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3e**, 2-(5-((4-fluorophenoxy) methyl) -1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3f** and 2-(5-((4-nitrophenoxy) methyl) -1,3,4-oxadiazol-2-ylsulfanyl) acetic acid **3g**.

The major objectives of this research work are: to calculate molecular parameters using DFT method, to build up QSAR model that investigate the cytotoxicity of the molecules under study and to calculate the free energy of interactions (binding affinity, ΔG) of the ligand with the receptor in the binding site through molecular docking.

Computational details

Molecular descriptors and ligand optimization

In present study, the optimization *via* quantum chemical method (DFT) of equilibrium geometries for seven molecular compounds was performed. Becke's gradients exchange correction (Becke, 1993) and the Lee, Yang, Parr correlation functional (*i.e.* B3LYP) (Lee *et al* 1988) are three parameters on which density functional theory method based on. Moreover, the exactness of density functional theory calculations is a function of basis set chosen. Thus, 6-31G** basis set was used for the optimization of the studied compounds so as to calculate descriptors which describe the bioactivity (IC₅₀) of the studied compounds. The optimizations of the compounds were achieved using quantum chemical software Spartan' 14 by wave function Inc (Spartan 14).

Furthermore, biological investigation on the molecules under study was carried out using the

obtained molecular parameters to build quantitative structure-activity relation (QSAR) model (Pourbasheer *et al* 2009). This was achieved with the aid of multiple linear regression method which is a recurrent statistical process used in making QSAR model. More so, the developed QSAR model was validated by observing some geometric equations such as cross validation (R^2) and adjusted R^2 (Equation 1 and 2).

$$CV.R^2 = 1 - \frac{\sum(obs - cal)^2}{\sum(obs - obs)^2} \quad (1)$$

The R^2 adjusted could be calculated using equation (2)

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

Moreover, the optimized molecular structures were also used for the study of docking to guesstimate binding affinity of the molecules to the *S. aureus* cell line, MTCC 121 receptor (PDB ID: 4b19).

RESULTS AND DISCUSSION

DFT calculation

This research work through B3LYP/6-31G** level of theory brought about several descriptors *i.e.* HOMO and LOMO energies, solvation energy,

polar surface area (PSA), dipole moment (DM), weight, Log P, Ovality and heteroatoms (average of electronic charges on all heteroatom in the compound) as shown in **Table 1** and these were used to define the cytotoxicity of the compounds. Agreeing to the theory of frontier molecular orbital, the bioactivity was affected by the highest occupied molecular orbital energy and lowest unoccupied molecular orbital energy (very imperative descriptors) (Mu *et al* 2015; 2016). The calculated HOMO energy are -6.46eV, -6.30eV, -5.94eV, -6.52eV, -6.52eV, -6.44eV, -6.14eV for **3a-g** while calculated LUMO energy are -0.85eV for **3a**, -0.82eV for **3b**, -0.78eV for **3c**, -0.99eV for **3d**, -1.03eV for **3e**, -0.90eV for **3f**, -0.89eV for **3g**.

Meanwhile, greater highest occupied molecular orbital energy shows the capability of a compound to bequeath electrons to adjoining receptor and equally, lesser lowest unoccupied molecular orbital energy enhances the knack of a molecule to admit electrons from the receptor.

Therefore, due to important role played by these two descriptors in the tie of molecules and enzymes, it is expected that the interactions that will occur be heightened, however, in this study, no fair correlation was established between the cytotoxicity of these compounds and the HOMO as well as the LUMO energies. More so, **Figure 2** shows HOMO-LUMO overlay.

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

	HOMO	LUMO	BG	DM (Debye)	SE (Kj/mol)	CH	CP	GN	LOG P
3a	-6.46	-0.85	5.61	4.54	-48.49	2.80	-3.66	2.38	3.20
3b	-6.30	-0.82	5.48	4.67	-47.41	2.74	-3.56	2.31	3.69
3c	-5.94	-0.78	5.16	3.90	-52.66	2.58	-3.36	2.19	3.07
3d	-6.52	-0.99	5.53	4.71	-46.76	2.77	-3.76	2.55	3.76
3e	-6.52	-1.03	5.49	4.65	-48.21	2.75	-3.76	2.57	4.03
3f	-6.44	-0.9	5.54	4.57	-42.20	2.77	-3.67	2.43	3.36
3g	-6.14	-0.89	5.25	4.68	-55.09	2.62	-3.52	2.35	2.84
	MW	OVALITY	PSA	HET	POL	HBA	HBD	<i>S. aureus</i> (MTCC 121)	
3a	252.25	1.41	68.15	-1.054	58.09	6	1	0.65	
3b	266.27	1.44	68.19	-1.054	59.60	6	1	0.60	
3c	282.27	1.46	75.14	-1.058	60.40	7	1	0.60	
3d	286.69	1.44	68.00	-1.059	59.22	6	1	0.55	
3e	331.14	1.44	68.07	-1.055	59.59	6	1	0.55	
3f	270.24	1.42	68.04	-1.061	58.48	6	1	0.45	
3g	299.26	1.48	116.63	-1.056	60.43	9	3	0.40	

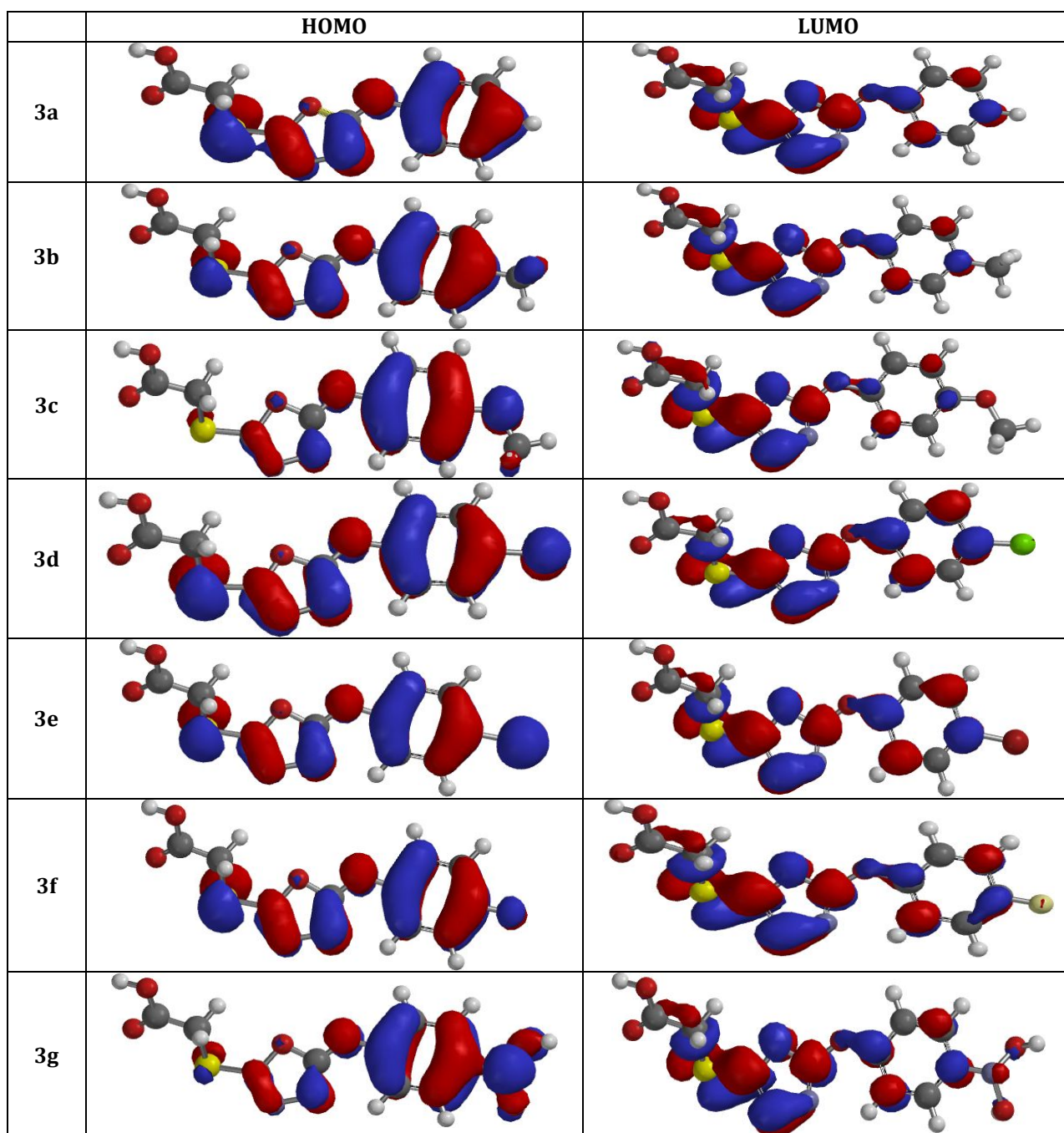


Fig. 2. HOMO-LUMO overlay

Moreover, the lower the band gap, the higher the capacity of a molecule to contribute electron(s) to the contiguous molecules. Therefore, the band-gap (LUMO energy - HOMO energy) which was calculated to be 5.61eV, 5.48eV, 5.16eV, 5.53eV, 5.49eV, 5.54eV, 5.25eV for **3a-g** as revealed in **Table 1** shows no correlation with the cytotoxicity of these compounds. Also, log P which was calculated to be 3.20, 3.69, 3.07, 3.76, 4.03, 3.36, 2.84 for **3a-g** reveal the ability of the compound to disband in lipophilic/non-aqueous solutions. Meanwhile, lipophilicity is dignified as the sharing of molecules between non-aqueous

and aqueous phase and it exposes the biological activity of molecules (Abass *et al* 2011), so it was noted that, in oral absorption of ligand, delinquency may possibly occur if Log P is higher than 5 (Meanwell, 2011). Therefore, all the compounds in this study are effective in term of lipophilicity, since they are not greater than 5. Furthermore, increased solvation energy could contribute to the drug opposition; thus, **3c** and **3g** were better in term of solvation energy. Also, it was reported that anomalous property of ligand is a function of huge value of dipole moment, so, **3a-g** were appropriate in term

dipole moment, since their dipole moment values are moderate. For polar surface area (PSA), all the compounds under study were orally active as it was noted that PSA should not surpass 120\AA^2 for drug that are orally energetic which were conveyed by trans cellular route (van de Waterbeemd *et al* 1998; Kelder *et al* 1999).

QSAR studies

The calculated parameters for seven molecular compounds functioned as independent variables, while the experimental inhibitory concentration (IC_{50} , μM) against *S. aureus* cells line acted as dependent variable in building QSAR model via multiple linear regression (MLR).

In study of quantitative structural activities relation, the fitness and ability to predict could be used to appraise the developed QSAR model. So, equation 3 was obtained via the developed model which replicated the observed IC_{50} as shown in **Figure 3** with fitting factor 0.995.

$$IC_{50} = 0.299 - 0.008(\text{HOMO}) - 0.009(\text{Log P}) - 0.028(\text{SE}) - 0.001(\text{MW}) - 0.128(\text{HBA}) \quad (3)$$

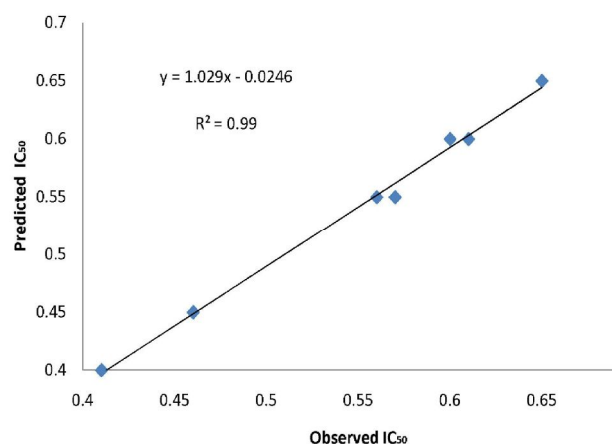


Fig. 3. Correlation between predicted and observed IC_{50}

Therefore, the combination of HOMO, Log P, Solvation energy, Molecular weight and HBA defined the anti-*S. aureus* activity of the studied compounds. More so, the performance of QSAR model cannot be adequately authenticated by using only fitting value (R^2), therefore, it is necessary to validate QSAR model by using geometric equation (cross validation (R^2) and Adjusted R^2) as shown in **Table 2**.

The obtained value for fitting factor (R^2) (0.998) showed that it fitted well. Also, the cross validation value ($CV.R^2$) (0.998) showed the

steadfastness of the developed QSAR model, because the value obtained was higher than 0.5 (Standard) (Ponce *et al* 2004).

Table 2. Statistical parameters for validation of QSAR model

N	p	R^2	$CV.R^2$	R^2_{adj}
7	5	0.998	0.998	0.988

More so, the calculated value for adjusted R^2 (0.988) exposed that the QSAR model is prognostic since the calculated value is greater than 0.6 (Standard) (**Table 2**).

Docking and scoring

Docking study was executed on the studied compounds coupled with bacteria cell line (PDB ID: 4b19) (Sayed *et al* 2012) which was obtained from protein data bank.

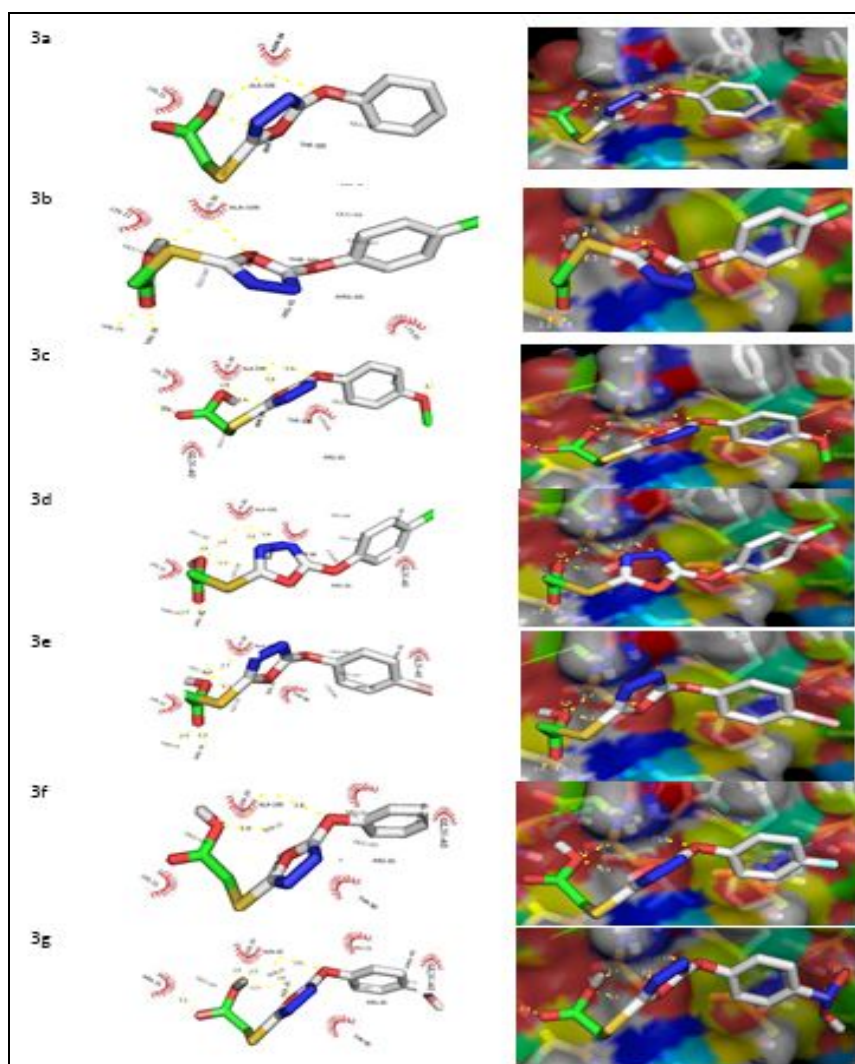
The docking study was accomplished by using several softwares (Discovery studio, Autodock tool, Autodock vina and Pymol as post-dock software).

Nine conformations were obtained from the docking simulation of individual compound and highest free binding energy (*i.e.* more negative value) in each docking simulation was assumed to be most stable. The calculated binding energy for compound **3a-g** were -4.5kcal/mol, -5.0kcal/mol, -4.7kcal/mol, -4.9kcal/mol, -4.9kcal/mol, -4.8kcal/mol and -4.9kcal/mol (**Table 3**).

In this study, several residues were involved in the interaction for the studied compound such as AGN-26, AGN-26, SER-25 and SER-25 with distance 2.8, 2.5, 2.5, 2.9 for **3a**, LYS-30, THR-29, SER-25, SER-25 and ARG-26 with 2.4, 2.2, 3.1, 2.5, 2.6, and 2.7 as distance for compound **3b**, for compound **3c**, ASN-28, SER-25, SER-25, ARG-26, ARG-26, ARG-26, ALA-18 with distance 3.1, 2.8, 2.4, 2.6, 2.9, 2.9, 3.1; SER-25, ARG-26, ARG-26, ARG-26, SER-25, LYS-30, THR-29, with 2.9, 2.8, 2.6, 2.8, 2.3, 2.3, 2.0 as distance for **3d**, LYS-30, THR-29, SER-25, SER-25, ARG-26, ARG-26, ARG-26, with 2.3, 2.0, 2.9, 2.1, 2.7, 2.8, 2.8 for compound **3e**, SER-25, SER-25, ARG-26, ARG-26, with 2.7, 2.6, 2.4, 2.8 for compound **3f**, and for compound **3g**, ASN-28, SER-25, SER-25, ARG-26, ARG-26, ARG-26, ALA-18, ALA-18, with 3.3, 2.8, 2.3, 2.5, 2.8, 2.8, 3.1, 2.9. Therefore, compound **3b** acted to be better in the interaction with 4b19 receptor in term of binding energy as shown in **Table 3**. The interaction between ligand and the receptor are shown in **Figure 4**.

Table 3. Interactions between ligands and 4b19 receptor

Compd	Affinity (kcal/mol)	H-Bond Between protein residues in the binding pocket and Drug	Distance
3a	-4.5	(i) AGN-26, LIG: O (ii) AGN-26, LIG:O (iii) SER-25, LIG:O (iv) SER-25, LIG:O	(i) 2.8 (ii) 2.5 (iii) 2.5 (iv) 2.9
3b	-5.0	(i) LYS-30, LIG: O (ii) THR-29 LIG:O (iii) SER-25, LIG:O (iv) SER-25, LIG: O (v) ARG-26 LIG:O (vi) ARG-26, LIG: O	(i)2.4, (ii) 2.2, (iii) 3.1, (iv) 2.5, (v) 2.6, (vi)2.7
3c	-4.7	(i) ASN-28, LIG: O (ii) SER-25, LIG:O (iii) SER-25, LIG:O (iv) ARG-26 LIG:O (v) ARG-26 LIG:O (vi) ARG-26 LIG:O (vii) ALA-18 LIG:O	(i) 3.1, (ii) 2.8, (iii) 2.4, (iv) 2.6, (v) 2.9, (vi) 2.9, (vii) 3.1
3d	-4.9	(i) SER-25 LIG:O (ii) ARG-26 LIG:O (iii) ARG-26 LIG:N (iv) ARG-26 LIG:N (v) SER-25 LIG: O (vi) LYS-30, LIG: O (vii) THR-29, LIG:O	(i) 2.9, (ii) 2.8, (iii) 2.6, (iv) 2.8, (v) 2.3, (vi) 2.3, (vii) 2.0
3e	-4.9	(i) LYS-30, LIG:O (ii) THR-29, LIG:O (iii) SER-25, LIG:O (iv) SER-25, LIG:O (v) ARG-26, LIG:O (vi) ARG-26, LIG:O (vii) ARG-26, LIG:O	(i) 2.3, (ii) 2.0, (iii) 2.9, (iv) 2.1, (v) 2.7, (vi) 2.8, (vii) 2.8
3f	-4.8	(i) SER-25, LIG:O (ii) SER-25, LIG:O (iii) ARG-26, LIG:O (iv) ARG-26, LIG:O	(i) 2.7, (ii) 2.6, (iii) 2.4, (iv) 2.8
3g	-4.9	(i) ASN-28, LIG: O (ii) SER-25, LIG:O (iii) SER-25, LIG:O (iv) ARG-26, LIG: O (v) ARG-26, LIG: O (vi) ARG-26, LIG: O (vii) ALA-18, LIG: O (viii) ALA-18, LIG: H	(i) 3.3, (ii) 2.8, (iii) 2.3, (iv) 2.5, (v) 2.8, (vi) 2.8, (vii) 3.1, (viii) 2.9

**Fig. 4.** Binding interaction of 3a-g with 4b19

CONCLUSION

In this study, calculation of molecular parameters via DFT method was achieved as well as the anti-bacterial activity of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids derivatives. The results of the QSAR study showed that certain parameters linked the

electronic properties of the studied compounds to their cytotoxicity, also the QSAR model replicated the observed bioactivities of these molecules against 4b19. Moreover, the results obtained from docking predicted stable conformations of the ligands within the enzyme's active cavity.

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