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Computational Studies of Some Hydrazone Derivatives as Antibacterial Agent: DFT and Docking Methods

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ABSTRACT

Quantum chemical calculations through density functional theory and docking study were carried out on a set of seven hydrazones and S. *aureus* cell line (4b19) so as to observe their inhibitory abilities of hydrazones. Many parameters which describe the anti- S. *aureus* were evaluated. All the compounds under study were docked against S. *aureus* cell line as receptors and the resulting binding energies reflected the extent of their binding affinities. 2,4-dinitrophenylhydrazone of formaldehyde showed the highest binding affinity.

Keyword: hydrazone derivatives, *S. aureus,* DFT, docking

INTRODUCTION

Many different bacteria cause various infections in man and animals. These infections are treated with the use of drugs. However, many bacteria have developed resistance to several antibiotics. This has led to the continued search for new drugs that could be effective as antibacterial. Hydrazones and their derivatives have provided a rich field for research of such new drugs [1].

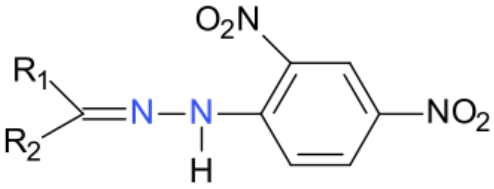
Hydrazones have been shown to exhibit different biological activities and to form metal complexes [2-7]. Such biological activities include anti-leprosy, antimicrobials, anti-tuberculosis, anti-tumor, and antihypertensive agents. These varied biological activities have drawn the attention of many researchers to the study of hydrazones [8].

In view of the time and cost of preparing compounds that might be useful as drugs, quantum chemical calculations including docking studies are increasingly being used to evaluate molecules that have drug-like properties with a view to minimizing waste of money, time and resources.

Docking study reveals the interaction between drug-like molecules and an enzyme (receptor) through identifying the suitable binding site in the enzyme. Several problems are encountered in the detection of drug-like compounds used for protein-protein interface target as well as the flexibility of proteins. The interactions calculated from docking experiment could be expressed in term of dock score. This is because scoring as a mathematical technique is used to envisage the power of the interaction that is non-covalent between two compounds once the docking is complete [9,10].

In view of this, quantum chemical method (QCM) via density functional theory (DFT) method and the calculation of binding energy for seven compounds as shown in Figure 1

were undertaken. The aim of this paper is to use DFT method to calculate molecular parameters that define the cytotoxicity of the studied molecules and to observe the interaction between both the ligand and the receptor (*S. aureus* cell line; PDB ID:4619).



	R_1	R_2
AB1	H	H
AB2	CH_3	CH_3
AB3	Ph	H
AB4	Ph	CH_3
AB5	Ph	Ph
AB6	Ph	CF_3
AB7	Ph	CPh_3

Figure 1. The schematic structures of hydrazone derivatives

EXPERIMENT

Computational details

Ligand Optimization and docking study

In this study, optimization of the structures of seven compounds in Figure 1 was performed through quantum chemical method using density functional theory (DFT). The three parameters on which density functional theory is based are Becke's gradients exchange correction [11] and the Lee, Yang, Parr correlation functional (*i.e.* B3LYP) [12]. Also, the accuracy of density functional theory calculations are based on the chosen basis set, hence, 6-31G* was the basis set used for the optimization of the seven molecular compounds and for the calculation of parameters that described the cytotoxicity of the compounds under study. The software used in this work was Spartan' 14 by wave function Inc [13]. In addition, the optimized structures for the studied molecular compounds were used for docking study so as to calculate the binding affinity of the molecular compounds to the *S. aureus* cell line (PDBID: 4b19). Inhibition constant was also calculated using equation 1:

$$K_i = e^{\frac{-\Delta G}{RT}} \qquad (1)$$

RESULT AND DISCUSSION

Molecular Descriptors

Molecular descriptors like E_{HOMO}, E_{LUMO}, dipole moment (DM), weight, hydrophobicity (Log P), volume (V), area, polar surface area (PSA), ovality, and heteroatoms (i.e. average of Mulliken charges on all heteroatoms in the compound) via B3LYP/6-31G* level of theory were obtained (Table 1).

According to frontier molecular orbital theory, both the highest occupied molecular orbital energy (E_{HOMO}) and the lowest unoccupied molecular orbital energy (E_{LUMO}) are very

important descriptors that affect the bioactivity of molecules [14, 15]. The calculated E_{HOMO} and E_{LUMO} values are given in Table 1.

High values E_{HOMO} indicate the ability of a molecular compound to donate electrons to neighboring molecules (enzyme) while low values E_{LUMO} improves the propensity of a compound to receive electrons from the molecules that have the ability to donate.

The value of E_{HOMO} is higher for the **AB5** molecule while the value of E_{LUMO} is lower for **AB6** molecules (Table 1). Hence, **AB5** is expected to release electron easily to the receptor with the tendency of better interaction. Also, **AB6** have the greatest tendency to accept an electron. The band gap values in Table 1 show that the **AB5** molecule has the lowest values (2.56eV). Oyebamiji et al., 2017 reported that the lower the band gap, the greater the ability of a molecular compound to donate electron(s) to the nearby molecules [16]. Therefore, **AB5** is expected to inhibit the receptor used in this study more than others.

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

	E_{HOMO}	E_{LUMO}	BG	DM	CH	CP	GN	LOG P	OVA	PSA	POL
AB1	-6.31	-2.79	3.52	9.69	1.76	-4.55	5.88	-5.66	1.38	99.15	55.29
AB2	-6.24	-3.43	2.81	12.00	1.40	-4.83	8.31	-4.77	1.44	96.87	58.52
AB3	-6.14	-3.44	2.70	12.08	1.35	-4.79	8.49	-3.19	1.47	96.24	62.39
AB4	-6.13	-3.42	2.71	12.28	1.35	-4.77	8.41	-3.62	1.50	96.22	63.86
AB5	-5.99	-3.43	2.56	12.04	1.28	-4.71	8.66	-1.73	1.56	95.55	69.20
AB6	-6.61	-3.50	3.11	11.58	1.55	-5.05	8.21	-2.48	1.53	96.58	64.94
AB7	-6.12	-2.91	3.21	8.86	1.60	-4.51	6.35	1.87	1.66	90.11	83.80

Lipophilicity (log P) shows the capacity of the compound to be soluble in lipophilic/non-aqueous solutions and also indicates the cytotoxicity of a compound. The calculated log P values given in Table 1 shows that the values of log P are less than 5. For oral administration of drugs, it is recommended that the value of lipophilicity of the drug-like molecule should not be greater than 5 [17, 18]. Therefore, all the molecules in this research meet the criterion for the oral administration of drugs. It was reported that unusual features of a drug-like molecule are based on the large value of dipole moment. Therefore, **AB1-AB7** molecules appear suitable in term of dipole moment values. This is because the calculated dipole moment values are moderate. In addition, polar surface area values should not be greater than $120A^2$ for a drug that are orally administered and are carried by trans-cellular route; thus, all the studied drug-like molecules maybe orally active [19-21]. Values of other descriptors like chemical hardness, chemical potential, global nucleophilicity, and ovality are calculated as shown in Table 1.

Docking and scoring

Molecular docking study was carried out on seven (7) molecules together with their receptors (**4b19**) [22] obtained from the protein data bank. In this study, some software (Discovery studio, Autodock tool, Autodock vina, and Pymol as the post-dock software) were used. Nine (9) conformations were observed for each individual interaction. The calculated binding energies for the molecules are shown in Table 2. According to Oyebamiji et al., 2017, the conformation with utmost binding energy (i.e. most negative value) have a higher tendency to be the best candidate to inhibit a receptor. Therefore, **AB7** with the highest binding affinity (Table 2) have the utmost capacity to inhibit the receptor (**4b19**). The

effectiveness of **AB7** was validated using equation 1 and it was observed that the compound (**AB7)** with lower affinity have higher inhibition constant (K_i). Similarly, the hydrogen bonds and hydrogen bond distance observed in the studied interaction are shown in Table 2. The binding mode of **AB7** (with the utmost binding energy) in the active site of 4b19 is displayed in Figure 2. The hydrophobic interactions between aromatic and PHE-19 (pi-pi interaction), as well as pi-alkyl interaction between aromatic and ALA-16 for compound **AB7**, were shown in Figure 3.

Table 2. Interactions between Ligands and receptor (4b19)

	Affinity (kcal/mol)	**K_i (µM)**	**H-Bond Between Amino Acid and Drug**	**Distance**
AB1	-4.2	$1.20x10^3$	(i) ARG-26, LIG: O (ii) LYS-30, LIG: O	(i)2.93 (ii) 3.01
AB2	-4.3	$1.42x10^3$	-	-
AB3	-5.3	$7.71x10^3$	(i) SER-13, LIG: O (ii) SER-13, LIG: O	(i) 2.31 (ii) 2.30
AB4	-4.8	$3.31x10^3$	(i) SER-13, LIG: O (ii) SER-13, LIG: O	(i) 2.89 (ii) 2.00
AB5	-5.9	$2.12x10^4$	-	-
AB6	-5.4	$9.13x10^3$	(i) SER-13, LIG: O (ii) SER-13, LIG: O	(i) 2.70 (ii) 2.24
AB7	-6.1	$2.97x10^4$	(i) ALA-16, LIG:H	(i) 2.69

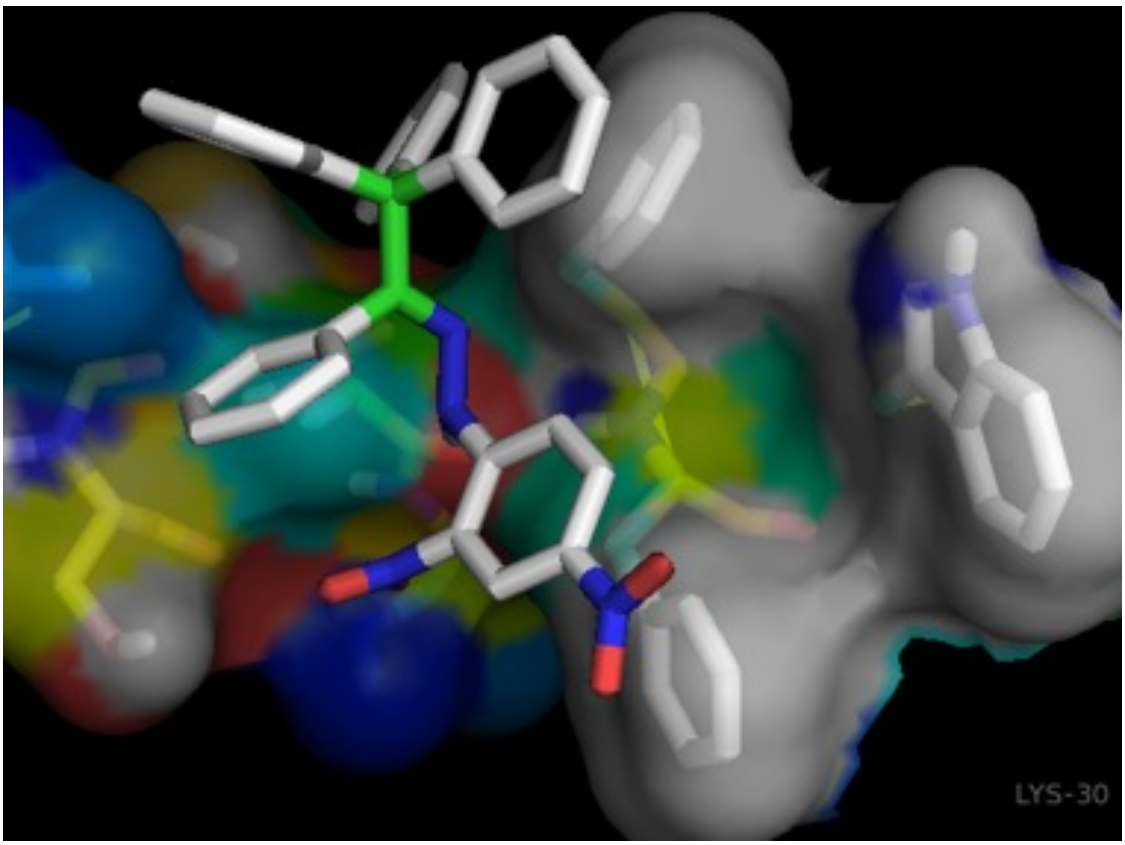


Figure 2. Binding interaction of compound **AB7** with **4b19**

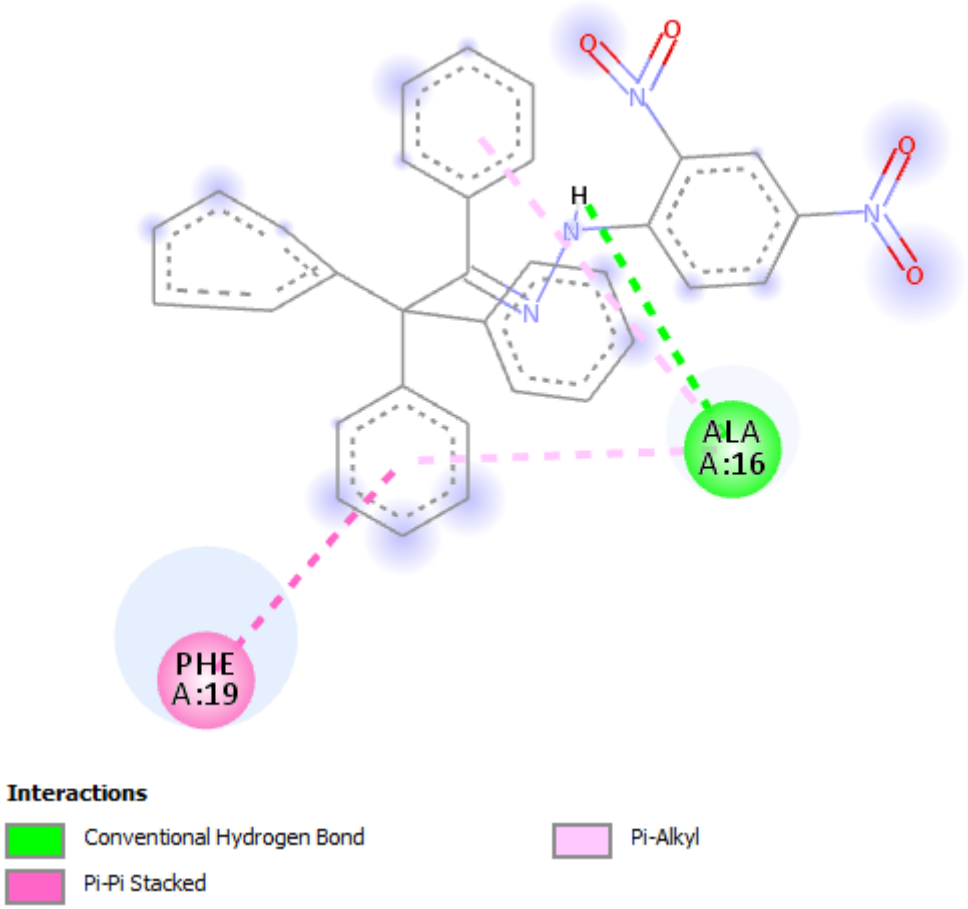


Figure 3. 2D structure for binding interaction of compound AB7 with 4b19

CONCLUSION

Quantum chemical method through DFT method was employed to verify anti-*S. aureus* activity of some hydrazine derivatives. Furthermore, the docking study predicted steady conformations of the ligands (Hydrazone derivatives) in the active site of the enzyme (4b19). Furthermore, the calculated binding energy for **AB7** indicates that the molecule has a greater ability to inhibit S. *aureus* than others and this was further validated by observing the inhibition constant.

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