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Computatonal 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.

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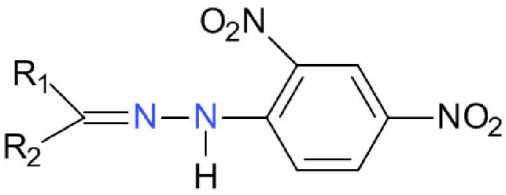
Introduction

Many different bacterial cause various infections in man and animals. These infections are treated by the use of drugs. However, very many bacteria have developed resistance to several antibiotics. This has led to the continuing search for new drugs that could be effective as antibacterial. Hydrazones and their derivatives have provided a rich field for search of such new drugs (Praven *et al.,* 2016).

Hydrazones have been shown to exhibit different biological activities and to form metal complexes (Ghazy et al., 2000; Kabil et al., 1999; Khalifa 1995; Jackson et al., 1990; Abdelkarim 2015; Sridhar et al., 2001). Such biological activities include anti-leprosy, antimicrobials, anti-tuberculosis, anti-tumor and anti-hypertensive agents. These varied biological activities have drawn attention of many researchers to the study of hydrazones (Josephp et al., 2016).

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 minimising wastage of money, time and resources.

Docking study reveal the interaction between drug-like molecules and an enzyme (receptor) through identifying the suitable binding site in the enzyme. Several problems are facing the detection of drug-like compounds used for protein – protein interface target as well as 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 are non-covalent between two compounds once the docking is complete (Jain et al., 2006; Taylor et al., 2002).



	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

Fig. 1. The schematic structures of hydrazone derivatives

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).

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 Becke 1993) and the Lee, Yang, Parr correlation functional (*i.e.* B3LYP) (Lee et al., 1988). Also, the accuracy of density functional theory calculations is based on the chosen basis set, hence, 6-31G* was the basis set used for the optimisation 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 (Spantan 14). 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 (PDB ID: 4b19).

3.0 Results and Discussion

3.1 *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 (Mu et al., 2015; Mu et al., 2016). 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 neighbouring 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 highest for the **AB5** molecule while the value of E_{LUMO} is lowest for **AB6** molecules (Table 1). Hence, **AB5** is expected to release more easily electron to the receptor and have the tendency to bring about better interaction. Also, **AB6** have the greatest tendency to accept electron. The band gap values in Table 1 show that **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	5.881392	-5.66	1.38	99.15	55.29
AB2	-6.24	-3.43	2.81	12	1.405	-4.835	8.319297	-4.77	1.44	96.87	58.52
AB3	-6.14	-3.44	2.70	12.08	1.35	-4.79	8.497815	-3.19	1.47	96.24	62.39
AB4	-6.13	-3.42	2.71	12.28	1.355	-4.775	8.413515	-3.62	1.5	96.22	63.86
AB5	-5.99	-3.43	2.56	12.04	1.28	-4.71	8.665664	-1.73	1.56	95.55	69.2
AB6	-6.61	-3.50	3.11	11.58	1.555	-5.055	8.216407	-2.48	1.53	96.58	64.94
AB7	-6.12	-2.91	3.21	8.86	1.605	-4.515	6.350537	1.87	1.66	90.11	83.8

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 show that the values of log P are less than 5. For oral administration of drug, it is recommended that the value of lipophilicity of the drug-like molecule should not be greater than 5 (Abass et al., 2011; Meanwell 2011). Therefore, all the molecules in this research meet the criterion for oral administration of drugs. Also, it was reported that unusual features of drug-like molecule is based on 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 drug that are orally administered and are carried by trans-cellular route; thus, all the studied drug-like molecules maybe orally active (van de Waterbeemd et al., 1998; Kelder et al.,

1999; Oyebamiji et al., 2018). 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 the seven (7) molecules together with the receptor (**4b19**) (saved et al., 2012) obtained from protein data bank. In this study, several softwares (Discovery studio, Autodock tool, Autodock vina and Pymol as the post-dock software) were used. Nine (9) conformations each were observed for 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 highest tendency to be the best candidate to bind to a receptor. Therefore, **AB7** with the highest binding affinity (Table 2) have the utmost capacity to inhibit the receptor (**4b19**). Similarly, the hydrogen bonds and hydrogen bond distance observed in the studied interaction are shown in Table 2. Also, 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)	H-Bond Between Amino Acid and Drug	Distance
AB1	-4.2	(i) ARG-26, LIG: O (ii) LYS-30, LIG: O	(i) 2.93 (ii) 3.01
AB2	-4.3	-	-
AB3	-5.3	(i) SER-13, LIG: O (ii) SER-13, LIG: O	(i) 2.31 (ii) 2.30
AB4	-4.8	(i) SER-13, LIG: O (ii) SER-13, LIG: O	(i) 2.89 (ii) 2.00
AB5	-5.9	-	-
AB6	-5.4	(i) SER-13, LIG: O (ii) SER-13, LIG: O	(i) 2.70 (ii) 2.24
AB7	-6.1	ALA-16, LIG:H	2.69

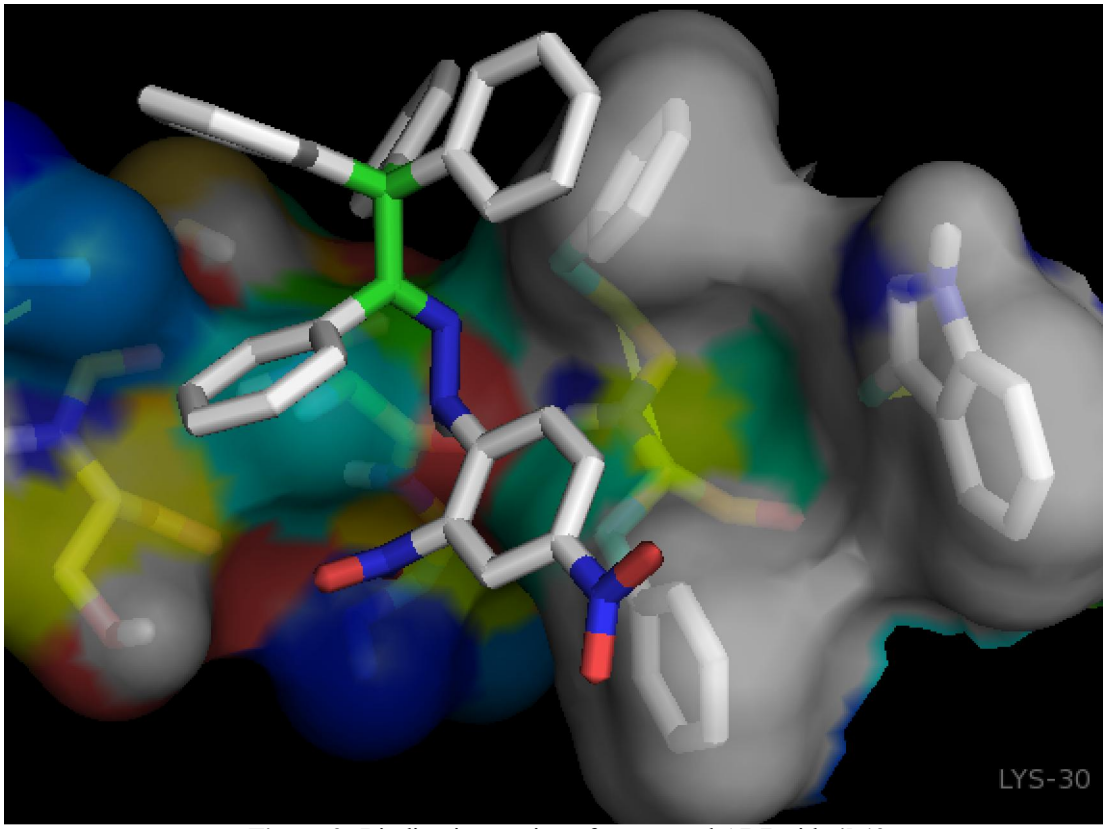


Figure 2: Binding interaction of compound **AB7** with **4b19**

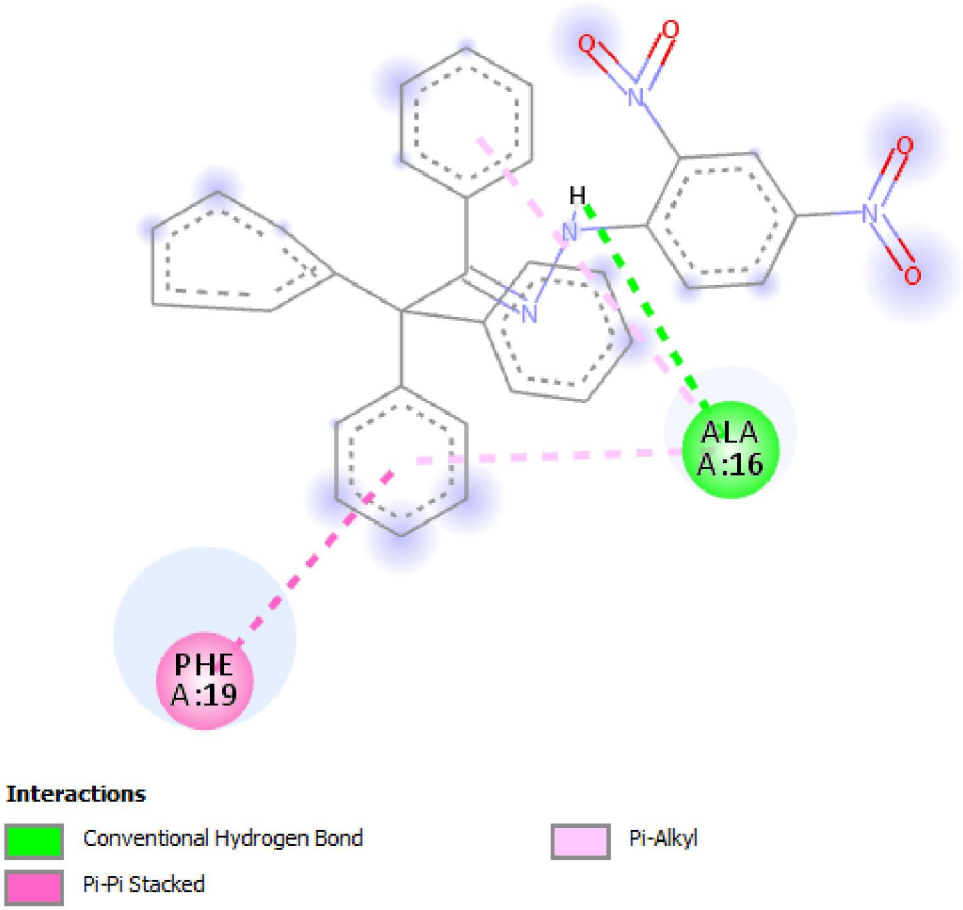


Figure 3: 2D structure for binding interaction of compound AB7 with 4b19

Conclusion

Quantum chemical method through DFT method was employed to verify anti-*S. aureus* activity of some hydrazine derivatives. Furthermore, the docking predicted steady conformations of the ligands (Hydrazone derivatives) in the active site of the enzyme (4b19). Also the calculated binding energy for **AB7** indicates that the molecule has the greatest ability to inhibit S. *aureus* than others.

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